Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis

PRELIMINARY OBSERVATIONS OF THE EFFECT OF HEPARIN UPON THE DISEASE*

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The description of intercapillary glomerulosclerosis by Kimmelstiel and Wilson[1] in 1936 directed attention to the pathological picture, and to the associated clinical syndrome present in advanced cases. It was soon realized that the incidence of the pathologic lesion is quite high in diabetics, varying from 18 to 63 per cent and that it is uncommon in the absence of diabetes, although it may occur. However, knowledge of the pathogenesis of this lesion has advanced little since its initial description. Hypertension and proteinuria are not causally related since they may be absent in early cases. Likewise, the severity of the diabetes, the use of insulin, sex and age do not appear to be important. However, there is an increased incidence of the lesion with increased duration of diabetes. Two other lesions are found in practically all cases of intercapillary glomerulosclerosis, these are retinopathy and advanced atherosclerosis. However, either may be present without any accompanying glomerulosclerosis.

An elevated blood cholesterol has been noted in a majority of the published cases, and doubly refractile lipoid droplets have been described in the urine.[2] Simon in 1940[3] described the frequent occurrence of fatty material in the glomeruli, but it remained for Wilens, Elster and Baker,[4] who have recently reported a thorough study of glomerular lipid in various kidney conditions, to suggest that the deposition of fat in glomeruli might be of primary importance in the development of the lesions of intercapillary glomerulosclerosis.

Recently the ultracentrifugal analysis of serum lipoproteins has been described.[5] This method allows the quantitative determination of lipoproteins as they actually exist in serum, with cholesterol, phospholipid, neutral fat and protein all linked together in large molecules. In view of the hypercholesterolemia found in many cases of the Kimmelsteil-Wilson syndrome and the increased glomerular lipid, the serum of seventeen

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patients with clinically typical diabetic glomerulosclerosis has been ultra centrifugally analyzed for lipoproteins.* Blood cholesterol, phospholipid, ratio of cholesterol to phospholipid, and the total lipids were determined at the same time.**

OBSERVATIONS IN 17 CASES

The clinical and laboratory findings in our first fourteen cases have been presented elsewhere,[6] and are shown in Table 1 and Table 2 plus data concerning the blood lipids and lipoproteins in three additional cases. (Five of our patients have died and the diagnosis was substantiated in the three instances in which autopsy was performed.) Table 3 shows the lipoprotein levels in our first fourteen cases compared with the mean lipoprotein values at comparable cholesterol levels in normals.

The serum cholesterol prior to the terminal state was below 300 mg. per 100 cc. in four patients. It was elevated in thirteen cases, as were the phospholipids in twelve. The ratio of cholesterol to phospholipids was elevated in eleven determinations.

The S_f 12-20 lipoproteins were markedly elevated in the entire series of patients. Furthermore, in all cases, these classes of lipoproteins were higher (by comparison with normals at the same cholesterol levels) than would be anticipated for the degree of elevation of the serum cholesterol. (Table 3) This shift toward marked increases in the S_f 12-20 levels was most striking in those patients whose blood cholesterol was below 300 mg. per 100 cc.

In most of the cases the S_f 20-35 lipoproteins were also elevated but in several they were not. However, the S_f 35-100 classes showed no such uniform tendency.

SIGNIFICANCE OF INCREASE IN S_f 12-20 LIPOPROTEINS

One of our cases illustrates a significant point. This was the only case in our series, which serial determinations of blood cholesterol and quantitative urinary protein excretion were available to us. This man, aged 29, had diabetes mellitus for thirteen years. He used 30 units of insulin daily and his diabetic control was fairly good. Mild hypertension had been present for two years, severe diabetic retinopathy for five years. His laboratory findings, exclusive of blood and urine sugar determinations, are presented in Table 4. His serum lipid abnormality antedated the albuminuria by at least two and a half years. Furthermore, doubly refractile fat bodies were present in the urine at the time albuminuria was first noted. In this patient at least, the data suggest that the lipid metabolic error preceded the kidney involvement.

Since the average duration of life after the first renal sign of diabetic glomerulosclerosis appears is six to seven years,[7] it would be valuable to have a diag-

* Ultracentrifugal analyses were performed at the Division of Medical Physics, Donner Laboratory, University of California, Berkeley.

** Cholesterol, phospholipid, and total lipids were determined at the Arteriosclerosis Research Laboratory of the Cedars of Lebanon Hospital, Los Angeles.
Cholesterol was analyzed by the Kingsley-Schaffert method. Phospholipid was determined as outlined by Peters and Van Slyke. Total lipids were measured by the turbidimetric method of Kunkel and Ahrens.

TABLE 1 Clinical findings in 17 cases of diabetic intercapillary glomerulosclerosis.

Patient	Age	Sex	Duration of diabetes	Blood pressure	Retinopathy Grades	Blood proteins			Fat bodies in urine	Albuminuria
						Total	Albumin	Globulin		
			Yrs.							
J.U.	48	M	10	230/120	2	5.6	2.6	3.0	Not done	5 gm./L.
W.L.	57	M	19	186/102	4	7.9			Present	3.1 gm./L.
G.S.	55	M	23	164/90	2	7.5			Present	6.9 gm./L.
E.G.	51	M	24	190/100	3	5.1			Present	6.9 gm./L.
P.B.	59	M	16	200/90	2	6.5			Present	1.8 gm./L.
B.A.*	34	F	15	140/90	4	6.1	2.5	2.6	Not done	Grade 4
J.F.	29	F	14	205/120	3	5.8	2.2	2.6	Present	Grade 4
W.K.	29	M	13	170/80	4	6.0	3.8	2.2	Present	3.8 gm./L.
M.R.*	48	F	20	250/114	4	5.0	2.5	2.5	Not done	Grade 4
R.R.*	27	M	20	180/110	2				Not done	Grade 3
J.C.*	34	M	15	200/120	3	5.1	2.9	2.2	Absent	Grade 4
C.I.	58	M	20	220/120	3	6.1	3.7	2.4	Present	4.2 gm./L.
E.K.W.	22	F	18	120/90	3	6.3	4.8	1.5	Present	Grade 3
E.N.	61	M	13	190/100	2	6.5			Present	5.7 gm./L.
D.N.	51	F	21	200/110	3	6.0	2.3	3.7	Present	Grade 4
D.G.	30	F	18	180/98	3	5.8	2.6	3.2	Present	Grade 3
S.K.	32	M	17	160/95	2	7.6	4.2	3.4	Present	1.6 gm./L.

*Intercapillary glomerulosclerosis found at autopsy.

TABLE 2 Serum lipids and lipoproteins in 17 cases of Kimmelstiel-Wilson syndrome.

Patient	Age	Sex	Chol-esterol	Phospho-lipid*	C/P ratio	S_f 12-20 lipo-proteins	S_f 20-35 lipo-proteins	S_f 35-100 lipo-proteins
W.K.	29	M	760	27.0	28.2	308	120	133
E.G.	51	M	389	13.2	29.5	121	29	40
E.W.	22	F	388	15.6	24.8	142	92	68
M.R.	58	F	580	26.5	21.8	319	190	230
B.A.[1]	34	F	282			182	145	99
B.A.[2]			171	8.6	19.9	152	81	86
E.N.	61	M	430	16.2	26.5	116	40	21
P.B.	59	M	389	14.0	27.8	116	61	21
W.L.	57	M	216	8.0	27.0	83	16	24
R.R.	27	M	274	11.8	23.2	100	57	64
J.U.	48	M	500	14.2	35.2	161	47	42
J.F.	29	F	389	12.8	30.4	116	40	81
C.I.	58	M	474	24.0	19.8	168	69	248
M.S.	55	M	340	11.7	29.0	71	48	52
J.C.[3]	34	M	369	14.3	25.8	237	159	173
J.C.[4]			296	12.4	23.8	145	100	161
J.C.[5]			180	8.1	22.2	95	84	81
D.N.	51	F	500	14.8	33.8	156	Not done	Not done
D.G.	30	F	455	16.5	27.5	104	Not done	Not done
S.K.	32	M	196	10.5	18.7	83	Not done	Not done

*Phospholipid values as determined before conversion to lecithin.

[1] July 22, 1952; [2] April 12, 1951; [3] January 24, 1951; [4] March 16, 1951; [5] April 13, 1951.

TABLE 3 Lipoprotein levels in Kimmelstiel-Wilson syndrome compared with the mean lipoprotein levels at comparable levels in normals.

Patient	Chol-esterol	S_f 12-20 Lipo-proteins	Mean S_f 12-20 Levels in Nor-mals at this Cholesterol Level	S_f 20-35 Lipo-proteins	Mean S_f 20-35 Levels in Nor-mals at this Cholesterol Level	S_f 35-100 Lipo-proteins	Mean S_f 35-100 Levels in Nor-mals at this Cholesterol Level
W.K.	760	308	Unavailable	120	Unavailable	133	Unavailable
E.G.	389	121	75	29	33	40	97
E.W.	388	142	75	92	33	68	97
M.R.	580	319	Unavailable	190	Unavailable	230	Unavailable
B.A. 7/22/50	282	182	51	145	31	99	70
B.A. 4/12/51	171	152	30	81	28	86	42
E.N.	430	116	82	40	34	21	107
P.B.	389	116	75	61	33	21	97
W.L.	216	83	40	16	29	24	53
R.R.	274	100	49	57	31	64	68
J.U.	500	161	96	47	34	42	124
J.F.	389	116	75	40	33	81	97
C.I.	474	168	90	69	35	248	118
G.S.	340	71	65	48	32	52	84
J.C. 1/24/51	369	237	70	159	33	173	91
J.C. 3/16/51	296	145	54	100	31	161	73
J.C. 4/13/51	180	95	32	84	29	81	44

nostic method available which might indicate the early development of this serious complication of diabetes. Some investigators feel that proteinuria is an early sign, others feel it is an indication of advanced renal disease and not necessarily indicative of glomerosclerosis. In the series reported by Mann, Gardner and Root, they found that cholesterol elevation occurred coincident with signs of renal involvement. Our data reveal marked elevation of the S_f 12-20 lipoproteins in this disease, occurring in some cases when the serum cholesterol was not elevated. Whether a rise in the concentration of this group of lipoproteins is an early finding in glomerulosclerosis remains to be determined in long term studies of diabetics. Our findings suggest this pos-

sibility. At this time the relationship, if any, between the S_f 12-20 lipoproteins and the alpha—2 golbulin which Rifkin and Petermann[8] found to be elevated in this disease is not clear.

The relation of glomerulosclerosis to renal arteriosclerosis has been the subject of considerable discussion. Advanced atherosclerotic disease has been present at autopsy in all cases. Elevation of certain serum lipoproteins is found in association with atherosclerotic disease and our data, showing an even greater elevation of these same classes of lipoproteins in diabetic glomerulosclerosis, further suggests a relationship between the two. However, renal atherosclerosis occurs in the absence of glomerulosclerosis. It has been shown[4] that when the kidney glomeruli contained considerable lipid material there was also a large amount of arteriolar lipid, but the latter could be demonstrated when no lipid was present in the glomeruli. Furthermore, intercapillary glomerulosclerosis is not found in myxedema, lipoid nephrosis or xanthoma tuberosum, diseases in which the S_f 12-20 serum lipoproteins are very high. These considerations suggest that whereas the elevation of certain serum lipoproteins is associated with both atherosclerosis and intercapillary glomerulosclerosis, in the latter there may be an additional glomerular factor present which facilitates the deposition of serum lipoproteins in the glomeruli.

THERAPY

The possibility that elevated S_f 12-20 and S_f 20-35 serum lipoproteins may be etiologically involved, at least in part, in the pathogenesis of the kidney lesion suggested that it was important to observe the effect of reducing the elevated lipoprotein levels upon the clinical course of the disease. This may be accomplished by a low fat diet, or by the injection of heparin.[9] One of us (H.E.) has given heparin* for the past six months to two patients with advanced diabetic glomerulosclerosis, and to one patient who probably has an early stage of the kidney lesion. Only preliminary observations will be presented at this time.

The first patient was a man, age 29, who had had diabetes for thirteen years, was hypertensive, and had been blind for five years because of diabetic retinopathy. He was markedly edematous, had albuminuria with doubly refractile lipoid droplets, a low serum albumin and markedly elevated blood lipids. His diabetic course was fairly stable on 30 units NPH insulin

* Supplied by Lederle Laboratories, Inc.

TABLE 4 Serial data in case of W.K.

Date	Cholesterol	Urinary Proteins in Grams	Serum Protein	Serum Creatinine	% of Normal Creatinine Excretion
4/29/47	592	0/24 hrs.	7.3		
10/10/47	391	0/24 hrs.			
8/24/48	310	0/24 hrs.			
4/6/49	472	0/24 hrs.	7.25	1.13	78
12/30/49	354	0.501/24 hrs. (oval fat bodies in urine)	6.5	0.96	70
9/8/50		1.03/24 hrs.	5.8	1.61	31
3/20/51	760	2.8/24 hrs.	5.6	1.4	

daily. He was placed in the hospital on August 18, 1951 for study, and during the first two weeks there was no change in the clinical picture on all types of diuretic therapy. He was then given (intravenously) 100 mg. heparin daily. After the first week his edema gradually decreased and disappeared. It is noteworthy that a discrete maculo-papular rash that had been resistant to therapy for several years cleared up within three weeks. After discharge on September 28, 1951, he was kept on 100 mg. heparin daily for two weeks and then it was given three times a week. After one month of this regimen the edema reaccumulated, the rash recurred somewhat, and he was readmitted to the hospital from December 24, 1951 to January 17, 1952. During this hospital stay he received all types of diuretic therapy with no improvement or weight loss. No heparin was given. After discharge he was again placed on 100 mg. heparin daily, and in three weeks he lost thirty pounds of edema fluid and the rash again disappeared. His laboratory findings are shown in Table 5. In this advanced case there was a slight decrease of proteinuria on daily heparin therapy, a slight rise in the blood albumin, and a marked drop in the S_f 12-20 lipoproteins with no change in the total cholesterol. When heparin therapy was reduced to 100 mg. three times a week, the proteinuria increased, the serum albumin fell slightly, the S_f 12-20 lipoproteins rose slightly, and clinically he became worse. When heparin was stopped, the serum albumin fell still further. Unfortunately the laboratory findings when daily heparin was resumed were lost.

The second patient was a man of 48 years with long standing diabetes, hypertension, retinopathy, marked albuminuria, high blood cholesterol (500 mg. per 100 cc) and very high S_f 12-20 lipoproteins (161 mg. per 100 cc). His laboratory data is presented in Table 6. Again on 100 mg. heparin daily there was a slight drop in the proteinuria, a subsequent increase when heparin was given three times a week, a marked rise when it

TABLE 5 W.K. variations in serum proteins, proteinuria and serum lipoproteins with heparin therapy.

Date	Alb.	Glob.	Protein-urea gms. in 24 hrs.	Proteinuria gms./1000 cc.	S_f 12-20	Chol.	P-L	Heparin Dose
8/20	2.7	2.4	3.4	1.41				None
8/29	2.6	2.6	3.3	1.40	164	750	24.0	
9/8	2.9	2.9	2.97	.99				100 mgm. I.V.
9/14			2.83	.87	62	900	26.0	daily from
9/20			2.22	1.05	73	750	18.0	8/30/51 to
9/28	3.0	2.8	2.6	1.18				10/12/51
10/24	3.5	2.4	4.1	2.4				100 mgm. 3x
11/30	2.8	2.1	3.0	1.82				weekly from
12/24	2.9	2.7	3.38	1.77	82	800	19.0	10/14 to 12/24
1/25	2.2	4.2	3.8	1:8				None from 12/24

TABLE 6 J.U. variation in serum albumin, globulin and proteinuria with heparin therapy.

Date	Alb.	Glob.	Protein-urea gms. in 24 hrs.	Proteinuria gms./1000 cc.	Heparin Dose
2/6	3.3	2.2	5.0	2.60	None
10/4	3.4	2.4	3.3	1.50	
10/10	4.1	2.2	5.72	2.20	100 mgm. I.V. daily from 10/8/51 to 11/11/51
10/17	4.1	2.4	3.66	1.95	
10/22			.845	1.14	
10/31	4.1	2.4	2.18	1.36	
11/9	4.8	2.2	2.1	1.34	
12/7			3.8	1.73	100 mgm. 3x weekly from 11/11 to 2/5
1/25	3.8	2.9	4.8	1.87	
4/4	3.8	2.6	8.7	3.0	None 2/5 - 4/4
5/7	3.6	2.3	5.39	2.58	100 mgm. 3x weekly 4/4 on

TABLE 7 S.K. variations in serum proteins and in proteinuria with heparin therapy.

Date	Alb.	Glob.	Protein-urea gms. in 24 hrs.	Proteinuria gms./1000 cc.	Heparin Dose
8/24	5.0	1.9	.335	.16	None
8/29	4.1	2.2	.386	.19	None
9/6	4.8	2.1	.871	.21	100 mg. I.V.
9/14	4.9	2.1	.259	.09	daily from
9/24			0	0	8/30/51 to
9/28	4.8	2.1	0	0	10/14/51
10/24	4.5	2.0	.312	.12	100 mg. I.V. 3x weekly from 10/12/51 to 1/25/52
11/30	4.4	1.9	.179	.05	
1/25/52	4.3	2.7	.30	.08	

was stopped, and very little change when he was again given 100 mg. heparin three times weekly. Unfortunately in this patient the lipoprotein changes on heparin therapy are not available.

The third patient, a 32-year-old diabetic of long standing, had early retinopathy, slight but persistent albuminaria, and a blood cholesterol of 196 mg. per 100 cc., but a high S_f 12-20 lipoprotein value of 83 mg. per 100 cc. Although admittedly a diagnosis of early glomerulosclerosis cannot be proven, heparin was given. The findings are presented in Table 7. There was a complete disappearance of albuminuria after several weeks of 100 mg. daily heparin, with a return of the proteinuria when the heparin dose was reduced to 100 mg. three times weekly although perhaps not to the former levels. Here again the lipoprotein changes after heparin are not available at this time.

Although the observations are few, from the laboratory standpoint there seems to be a tendency for proteinuria, in cases of diabetic glomerulosclerosis, to decrease slightly with heparin therapy. Apparently 100 mg. heparin daily is necessary for at least several weeks before this occurs.

In one patient there was clinically a remarkable decrease of edema on two occasions when all other types of therapy had failed. A long standing skin rash, previously resistant to therapy, disappeared after heparin was given for several weeks. (It should also be noted that in one of these patients, as in several other diabetics with atherosclerotic disease, there apparently was a decrease in insulin requirements while on heparin.) We feel that the improvements seen are related to the effect of heparin on the serum lipoproteins. Incidentally no untoward reactions were noted after six months of heparin therapy intravenously or subcutaneously. Lee-White clotting times returned to normal in six hours in all instances so that their routine determination is unnecessary.

We have observed the effect of a rigid low fat diet in only one case thus far. This is patient J. C. in Table 2. It can be seen that there was a progressive drop in the serum lipids and lipoproteins over several months. The cholesterol fell from 369 mg. per 100 cc. to 296 and then to 180. The S_f 12-20 lipoproteins fell from 237 mg. per 100 cc. to 145 and finally to 95 which is

still quite high. This patient was in preterminal uremia, however, so that it is not certain that the effects observed were due to the diet.

It is apparent that much further investigation is required before conclusions can be drawn as to the long term effects in diabetic glomerulosclerosis of these therapeutic means directed at lowering the S_f 12-20 and S_f 20-100 lipoproteins. It should be emphasized that any considerable reversal of previously existing disease cannot be anticipated. The most that one could expect is a cessation of, or at least a reduction in the rate of progression of the disease. However, any definite and maintained evidence of improvement in kidney function, even though slight, would indicate improvement in existing disease, and give rise to reasonable hope of arresting the progress of the disease. Our very preliminary observations are encouraging in this regard.

SUMMARY

The serum cholesterol, phospholipids, total lipids, and the S_f 12-20, 20-35 and 35-100 lipoproteins ultracentrifugally analyzed, have been determined in 17 cases of diabetic glomerulosclerosis. Elevated cholesterol and phospholipids were found in most of the cases. The most striking finding was a marked elevation of the S_f 12-20 class of lipoproteins in all cases, and of the S_f 20-35 class in nearly all patients. These lipoproteins were markedly elevated even when the cholesterol was normal. Furthermore the elevation of the S_f 12-20 lipoproteins was higher than would be expected at the elevated cholesterol levels. The data suggests that these classes of serum lipoproteins may be important, along with other factors, in the production of the kidney lesion. It is also suggested that elevated S_f 12-20 lipoproteins may be an early finding indicative of the potential development of glomerulosclerosis.

Heparin, which markedly reduces the S_f 12-100 classes of lipoproteins, has been given for six months in three cases of diabetic glomerulosclerosis. When administered in doses of 100 mg. daily, a reduction of S_f 12-20 lipoproteins occurred. There was a slight elevation in the serum albumin where it initially was low. There was a striking improvement clinically. These preliminary results are encouraging. We believe that clinical trial with long term heparin administration, and/or the low fat diet, are indicated since reduction of the serum S_f 12-100 lipoproteins may arrest the progress of this fatal kidney complication of diabetes.

DISCUSSION

DR. ALEXANDER MARBLE, (*Boston*): In June, 1950 I was privileged to visit Dr. Gofman in his laboratories in Berkeley. There were many others who did so at that time. I was impressed with his enthusiasm for large-scale studies, the organization and equipment of his laboratories and the amount of activity going on. At that time, two years ago, most of us knew scarcely anything about lipoproteins and the talk about S_f 12-20 and other classes of lipoproteins seemed a foreign jargon. Today we speak freely of such matters but often our knowledge is more superficial than we would like it to be. We are indeed indebted to Dr. Gofman and his associates in bringing to the attention of the profession, the probable relationship of large lipoprotein molecules to the development of atherosclerosis.

It is fitting that the studies in certain laboratories during the past two years have included diabetic patients. Indeed, in Dr. Gofman's early clinical observations he reported upon measurements in diabetic individuals and called attention to the need for further data in this regard.

As is well known to you and Dr. Gofman, his reports have met with varying degrees of acceptance. Some have maintained that the level of the blood cholesterol affords as good or better index of present or future atherosclerosis and its sequelae than does an abnormal lipoprotein pattern. There have been other objections which have been discussed or hinted at today. However, the results reported by Dr. Engelberg, Dr. Barach and Dr. Keiding with diabetic patients do suggest a definite correlation between the level of certain classes of lipoproteins and the degree of control of diabetes and complications in the patient. All will admit that present impressions are subject to change or revision as further data are accumulated.

The paper of Drs. Engelberg, Jones and Gofman is of great interest to us since their findings in patients with diabetic nephropathy are consistent with those of our group as just reported by Dr. Keiding. Indeed, in a paper published in 1949, Dr. Root along with Drs. Mann and Gardner reported an increase in the blood cholesterol in all but 3 of 22 patients with intercapillary glomerulosclerosis.

I noted that Dr. Engelberg stated that his patient W. K. had had well controlled diabetes and yet displayed persistent hypercholesteremia. I wonder if in this case familial hypercholesteremia had been ruled out?

Dr. Engelberg's report of his current studies with

heparin on patients with intercapillary glomerulosclerosis is instructive and we will await with interest results regarding the effect of heparin on this and other states in which an abnormal lipoprotein pattern exists.

It is worthwhile to call attention again to one finding which has emerged from the work in Boston which Dr. Keiding reported. I refer to the relationship between retinitis and the incidence of elevated values for the S_f 12-20 lipoproteins. Arterial calcification showed a much less striking relationship. One must admit, however, that arteriosclerosis of medial type as shown by x-ray in our studies may, at least theoretically, not parallel the degree of atherosclerosis which is much more difficult to assay in a study such as ours. However, the fact that there was a strong positive correlation between retinitis—which is an unique and early manifestation—and abnormal lipoprotein pattern is of especial interest, since it suggests some common basis for the origin of late vascular sequelae in the diabetic in the eyes, arteries and kidneys. As to the exact mechanism of this, and just what factors are primary and what secondary, we can only speculate at the present time. Furthermore, arterial disease should not be considered in terms of lipoids alone to the exclusion of other factors such as the physico-chemical characteristics of the so-called "ground substance." Not to be forgotten is the possible role of disturbance of the metabolism or structural organization of the complex mucopolysaccharides. Clarification of these problems must await further study.

DR. ROBERT L. JACKSON (*Iowa City, Iowa*): As Dr. Marble just mentioned, I agree that there is a need for serial determinations to elucidate this problem.

We have observed that our group of diabetic patients who maintain an excellent or good level of control have approximately normal serum cholesterol values, and that our group of patients in fair or poor control have marked fluctuations in serum cholesterol values. The cholesterol values were evaluated on the basis of serial determinations, and the level of control of the good or excellent group is considerably higher than for any group reported here today. The importance of using objective criteria for establishing level of control cannot be overemphasized.

In some cases with serial cholesterol determinations we have noted a significant lowering of the cholesterol value at the time of or after, a severe or mild infection. Temporary fluctuations in cholesterol levels may account for the occasional observation of a normal or low cholesterol value in association with a high S_f 12-20 lipoprotein value.

DR. JOHN W. GOFMAN (*Berkeley, California*): It is a source of considerable personal satisfaction to me to see, some two and one-half years after the original investigations of the ultracentrifuge method of studying lipoproteins, a society like the Diabetes Association presenting four papers of great clinical significance, associating such important problems as control of diabetes and vascular complications to lipid measurement.

Dr. Hanig has pointed out that if one excludes those diabetics who have the Kimmelstiel-Wilson syndrome and those with vascular disease, and outlying high values, the net average is not too much greater—if at all greater—than the average for so-called normals. I think this may be a little misleading. Actually, what are we after in a study of diabetics with respect to lipoproteins or cholesterol level? We are after a very specific answer. Is it something about diabetes itself which predisposes to vascular complications, or is it something about the lipid metabolism of diabetes which predisposes to vascular complications?

Now this is a matter of some concern, because if it is not just the lipid factor, we have to look at such possibilities as focal factors in the structure of arteries and such items as these in the effort to explain the increased incidence of vascular disease among our diabetic population. I do not think that any of the evidence that we have obtained, or the evidence Dr. Hanig has obtained, has disagreed but in one respect, and that is that there are certainly many diabetics, a large proportion of them, who have what we have to call perfectly normal or low lipoprotein levels. I think this is agreed, and I think it would be pretty hard, clinically, to prove that all diabetics develop excessive vascular disease. What we really can say is that diabetics develop more vascular diseases than the average population. We also know they may go a long time without developing clinical vascular disease. Therefore, if we exclude from our population all the diabetics who have manifested vascular disease from our study of lipoproteins, we are going to leave over a residue of diabetics who should closely correspond to our normal population, if we assume that the lipoproteins, alone, represent the factor predisposing the diabetics to vascular disease.

I should prefer to see Dr. Hanig's data presented with all the diabetics with vascular disease, the extremes included, and the Kimmelstiel-Wilson patients

included, because if we exclude all these patients, we are excluding those who have already manifested the very thing we are trying to find out if diabetics are predisposed to, namely: vascular disease. I think this obscures the situation to some extent, but in no way obscures the significance of his data.

With respect to Dr. Barach's paper, I was much interested in seeing his finding of the higher incidence of high values of S_f 12-20 lipoproteins in female diabetics as compared with males. I must say that our data are on a much smaller scale in diabetics than Dr. Barach's. Our preliminary data showed this same finding, and in the clinical literature there are several reports to the effect that female patients with diabetes develop vascular complications in excess of those experienced by males. Accordingly, then, this finding of Dr. Barach's would be consistent with the elevated lipoprotein level being a prime factor in accounting for the excessive vascular disease in females as compared with males.

The data which he found in diabetes and obesity—namely, that there is no elevation of the S_f 12-20 level in diabetic obese patients as compared with diabetic non-obese patients—is something we have never tested. In normals we find that obesity definitely does predispose to an elevated level of the S_f 12-20, and even more, to elevated levels of lipoproteins from S_f 20 to 100. However, this relationship, even in normals, is a very low one. While there are average trends in one direction, it is still true that there are many very lean individuals with high levels and many obese individuals with low levels.

In the papers by both Dr. Keiding and Dr. Barach I think a very important point was struck upon which I realize is controversial among the experts on diabetes, namely: "Will we reduce vascular complications by good control of our diabetics?" Both of these papers indicated that at least for this group of lipoproteins—which we have good evidence are associated with vascul disease—there is definitely a trend toward higher levels of these lipoproteins in the patients with poor control. I think this finding by both groups of workers is of great importance.

I made a quick statistical calculation on Dr. Keiding's data as shown on the slides, and one can reach a fair conclusion. He said that the lipoproteins showed a very different picture from the cholesterol. This, as many of you know, is something that we have claimed for some time, and which has been contested by some people. Actually, with Dr. Keiding's data, I believe we can say that the elevation of 12-20 lipoproteins and the elevation of the 20-100 lipoproteins is the complete story of the difference between his retinitis cases and the non-retinitis cases; one could show by calculation that the slight elevation in cholesterol—or even moderate elevation in cholesterol—is only that which would be expected for the elevation in these particular lipoproteins, in this particular class of lipoproteins. It should be emphasized again that now that we have methods for looking at all the forms of cholesterol in the blood, we cannot any longer be satisfied to lump them all together and to say that this is the *total* cholesterol or the *total* lipoproteins.

We are interested in knowing—in a diabetic as well as any other patient—what is the nature of this disturbance which causes these patients to have an elevation at one particular region. For instance, in Dr. Engelberg's paper, he pointed out that the Kimmelstiel-Wilson patient has an elevation in the 12 to 35 region, but not so much in the 35-100, indicating that lipid metabolism in the control of serum transport, at least, is a rather complicated thing, and that these subfractions can differ from one diease entity to another. For example, we have seen these pictures differ in the diabetic in acidosis as compared with the diabetic with Kimmelstiel-Wilson disease. Although two patients may have 500 milligrams per cent of blood cholesterol, their lipoprotein patterns are just as different as night and day in many terms of which classes of lipoproteins are elevated. This simply indicates that what we need to know is something about the metabolic factors that control the transformation of one lipoprotein into another, and thus explain why some are elevated in certain diseases.

DR. ENGELBERG (Closing): In answer to Dr. Marble, the serial data, as we said, are incomplete. In one patient, available data did suggest that elevated serum lipoproteins antedated signs of kidney involvement. Of course, considerable further study is necessary.

We feel that since increased glomerular lipid has been found in Kimmelstiel-Wilson disease, and we have found increased serum lipoproteins, it suggests that the serum lipoproteins are the source of the glomerular lipids, and are probably one of the factors involved in the progression of the pathological picture.

About the use of heparin, it is certainly our feeling at this time that it is clearly experimental. However, the preliminary findings are somewhat suggestive, and the fact that heparin is a physiological substance which

reduces large lipoprotein molecules to smaller molecules of a more normal type suggests its use in an attempt to delay the progress of this disease.

In the use of heparin in these cases, or in a much larger series of cases of atherosclerosis, we have not encountered any serious complications, because the anticoagulant factor is of short duration (approximately six hours following each injection). Minor complications such as sensitivity reactions and lumbar pain are easily avoided by changing the brands of heparin used.

However, I want to reiterate that it is our feeling that this is purely experimental therapy, and much further study is needed before conclusions can be reached.

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A Seasonable Gift for the Editors

Here is what the editors would like for Christmas—and indeed for the whole New Year.

They would like to receive a reasonable number of topflight new manuscripts, perhaps 250, from which they could make their choice, containing 800 to 4,000 words each, recently typed with double or triple spacing (including the case reports, footnotes and references), with a reasonably fresh ribbon. They would like to have the references limited to those of real significance, following accurately the style of the Cumulative Quarterly Index Medicus. *(The only impression that "inflated bibliographies" make is a bad one.)*

Needless to say, perhaps, any paper that is fit to be published is written in as good English as the author can muster, and is then rewritten at least twice, with a number of words discarded at each writing; for anything that is worth saying at all is usually said twice as well in half the number of words. Its tables and charts are few and simple and properly captioned. In its final state it is crystal-clear and informative and meets some need other than that of the author for publicity.

After all, the only really valid reason for writing a scientific medical article is to present the results of useful investigation or seasoned experience, thus adding to the sum of medical knowledge; or to bring together and correlate existing knowledge in order to make it more easily available. Only occasionally is a single case worth reporting, to remind the Journal's readers of the existence of some condition that may cause diagnostic confusion or to add to the knowledge of its treatment; it should be reported with the utmost brevity. A case report should always point the moral, whether or not it may adorn a tale.

The editors would like to find in their stockings the promise of a series of inspired and carefully worded editorials on a variety of pertinent subjects, and a salty but amiable correspondence suitable for publication. They would be pleased with a strict observance of deadlines on all promised material. Given these things, a circulation that continues to expand and a growing list of contented advertisers, they would believe that there really is a Santa Claus!

—*Editorial,* New England Journal of Medicine, *December 20, 1951*

Serum Lipoproteins and Cholesterol Levels in Normal Subjects and in Young Patients with Diabetes in Relation to Vascular Complications.*

Nils R. Keiding, M.D., George V. Mann, M.D., Howard F. Root, M.D., Eleanor Y. Lawry, Ph.D., Alexander Marble, M.D.

BOSTON, MASSACHUSETTS

The present study is concerned with the lipoprotein and cholesterol content of the blood serum in relation to diabetes of long duration and its characteristic complications. It has become increasingly evident that although young diabetic patients may survive under insulin treatment for 10 to 15 years without difficulty, thereafter generalized vascular disease, particularly with lesions in the eyes and kidneys, becomes distressingly frequent. These patients offer an unusual opportunity for the study of the nature of arteriosclerosis, uncomplicated by other chronic diseases frequently present in older subjects. A long-term study designed to assess the relationship between the degree of control of diabetes by means of insulin and diet and the frequency or severity of these complications, has been in progress in this clinic for several years.[1,2,3,4] Since the observations by Gofman[5] relating certain of the lipoproteins in the blood serum to such vascular changes as are concerned in coronary atherosclerosis, the application of this method of study to young diabetic patients long known to develop premature atherosclerosis, retinal lesions and nephropathy, seemed a necessary step. It appeared of particular importance to compare this new lipoprotein measurement with the simpler cholesterol determination in respect to their relation to the clinical manifestations of atherosclerosis.

LABORATORY METHODS

Lipoprotein determinations were done by the technic of Gofman and others[6] and cholesterol determinations by the method of Abell, Levy, Brodie and Kendall.[7] The reliability of these methods has been carefully determined by serial introduction of blind replicate samples. Such data collected over the 18 months of the present study reveal the following standard errors of duplicate differences: Total cholesterol 10.7 mg. per cent; lipoproteins, S_f 12-20, 4.9 mg. per cent, S_f 21-35, 3.1 mg. per cent, and S_f 35-100, 7.7 mg. per cent.

*From the Joslin Clinic; the Baker Clinic Research Laboratory, New England Deaconess Hospital; and the Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts.

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CLINICAL MATERIAL

A group of 218 diabetic patients has been studied. Of this number, 144 patients whose diabetes began between the ages of 1 and 30 years and was of at least 10 years duration, were selected for particular study in order to assess the relationship between laboratory findings, the control of diabetes and the development of complications. It should be pointed out that any such series of patients alive for periods of 10 to 36 years after the onset of diabetes is, by that very fact, a selected group. Follow-up surveys reveal that 25 per cent of 6,000 patients similar in age at onset of diabetes and observed during this same period of years have died chiefly of diabetic complications such as diabetic coma, pyelonephritis, diabetic nephropathy and tuberculosis. The smaller group of 144 patients was obtained by calling back for special study as out-patients those living within a reasonable distance of Boston and, secondly, by utilizing such patients as met the requirements who during this period were admitted to the New England Deaconess Hospital. In the total of 144 cases, 110 were patients who had been thus recalled and 34 were patients seen in the hospital. It is well to point out that these patients were not selected because they had been under our frequent observation. Actually, an outstanding feature of this follow-up was the discovery that patients whom we had first seen 15 or 20 years ago and who we thought were under observation by their own family doctors had, in many cases, ceased to see any doctor. Many patients admitted that, having found that they could feel well and maintain their weight by taking insulin alone without medical advice, had sought no professional care for periods of 5 to 10 or more years.

Each patient came to the office after an overnight fast and blood was drawn for determination of glucose, non-protein nitrogen, serum lipoprotein and cholesterol. In addition, x-ray examination of the arteries of the legs, the pelvis, a lateral film of the aorta and a chest film were made. A physical examination was made with special attention to the presence of neuropathy, exemplified by postural hypotension, loss of reflexes, muscular atrophy and hypesthesia. The patient was sent to an ophthalmologist for a complete examination of the eyes. In addition, a careful and prolonged interview was held with the patient in order to obtain detailed information concerning dietary practices, the amount of insulin taken and the frequency of medical examinations and laboratory tests during each of the 5 year periods of the total duration of diabetes.

CLINICAL CRITERIA

Based on the interview and information from the patient's record the case was classified according to one of three standards of control.

Details concerning the classification are given in a previous article.[4]

GOOD CONTROL 1. The patient must never have been in coma except in those instances in which the initial diagnosis of diabetes was made in coma. 2. Insulin therapy was begun within a few weeks after the onset of diabetes. 3. Urine tests for sugar were made at least once daily ever since onset of diabetes with a conscientious attempt to have the urine sugar free or nearly so before meals. Insulin dosage adjustments were made according to results of urine tests. 4. The diet must have been weighed for the first 6 weeks of treatment and thereafter at intervals with careful measurement of food at all other times since onset of diabetes. 5. Regular physical examinations and laboratory tests were made by a physician at least once annually. The blood and urine tests were satisfactory.

FAIR CONTROL 1. The patient must never have been in coma (except for cases in which the diagnosis was made with the patient in coma, or rare cases in which an unavoidable overwhelming infection or other complication precipitated coma). 2. Insulin therapy was begun within 24 months of onset of symptoms of diabetes. 3. Tests of the urine for sugar were made one or more times weekly in an attempt to maintain freedom from glycosuria. 4. Dietary management by the patient must have been conscientiously attempted, although food was not weighed or measured. Rarely, if ever, was there indulgence in gross dietary indiscretions. 5. Satisfactory blood sugar determinations were made at the time of physical examination by the patient's doctor at least once every 2 years.

POOR CONTROL 1. Avoidable coma one or more times. 2. Insulin therapy was not begun until more than 24 months after the onset of diabetes and in some cases used irregularly. 3. Urine specimens were tested infrequently, or at intervals of months or years. 4. No measurement or weighing of food was made in relation to urine tests or insulin dosage. 5. No regular examinations were made by a physician. At infrequent intervals, office or hospital examination showed marked glycosuria and hyperglycemia.

The diagnosis of retinitis was made in patients in whom many hemorrhages and exudates or actual retinitis proliferans were found. The group of patients with "no retinitis" included those with no hemorrhages whatever or only a minimal number such as 2 or 3 hemorrhages or microaneurisms. Similarly, patients were classified as having calcified vessels when parallel linear

areas of calcification were seen in more than one area and as having "no calcification" when either no evidence of calcification or only the most minimal traces were seen by roentgenogram. The diagnosis of diabetic nephropathy was based upon the finding of proteinuria, edema, hypertension and decreased kidney function; almost invariably there was associated retinitis of moderate or severe degree.

For comparative purposes data obtained from a control group of "normal" individuals have been included. These subjects were selected according to criteria established in the Cooperative Study of Lipoproteins and Atherosclerosis. In brief, subjects were obtained from industrial and business employment rolls and from clinic and hospital contacts of people obtaining annual physical check-up for preventive medical purposes. The clinical classification "normal" was based in each instance on: a negative medical history coupled with no physical and laboratory signs suggesting cardiovascular-renal disease or diabetes; blood pressure under 140/90; a normal electrocardiogram; and absence of protein, sugar or abnormal sediment in the urine. In addition, subjects with such disorders as thyroid disease, xanthomatosis, etc., were excluded when known. This group then serves as a reference for comparison. The term "normal" is applied to these data in the sense of prevalence and without implication of desirability.

RESULTS

The data on lipid levels in the normal group are contained in Table I. It is noteworthy that the values for each quantity are generally lower than the published data of Jones, et al.[8] Furthermore, the differences are larger than can be accounted for by the small but persistent difference of mean values consistently observed between laboratories in the Cooperative Study.*

The lipid levels in the total series of 218 diabetic patients with relation to age, sex, insulin dose and duration of the disease have been summarized in Figures 1a, 1b, 2 and 3. It appears that the concentration of serum lipoproteins of the S_f 12-20 class rises slightly with age but then has a tendency to fall slightly late in life. These changes are not dissimilar from those of the normal group. (Table I) The sex difference is not

* Since the subjects measured in each laboratory are obtained from similarly distributed sources (e. g., the Harvard Laboratory measurements include subjects from several California industries and the Donner laboratory group has measured many Massachusetts subjects), it seems unlikely that geographic differences explain the differences observed. For the present comparative purposes, these laboratory differences are of no particular significance.

TABLE I The serum cholesterol and lipoprotein levels of 704 normal Americans according to age and sex. Values are expressed in mg. per cent followed by standard deviation of distribution.

Age, decades	20-29	30-39	40-49	50-59	60-69	70-79	80-	Total
MALES								
Number of subjects	38	142	225	144	38	12	5	604
S_f 12-20	33.7 ±22.4	37.3 ±21.5	38.1 ±20	39.3 ±18.4	36.6 ±22	37.5 ±25.9	33 ±13.3	
S_f 21-35	21.3 ±21.6	29.9 ±14.4	21.9 ±16.3	22.5 ±13.4	19.1 ±11.7	24.2 ±15	21 ± 8	
S_f 35-100	60 ±51.1	59.3 ±42.2	65 ±52.3	59.1 ±46	50.3 ±37.3	51.7 ±54.9	36 ±21.3	
Total Cholesterol	219.7 ±80	227.5 ±59.5	238.8 ±59.5	236.5 ±51.5	227.6 ±51	195.8 ±51.5	215 ±37.5	
FEMALES								
Number of subjects	19	16	30	16	5	1		87
S_f 12-20	24 ±17.9	26.9 ±10.1	32.7 ±23.2	39.4 ±17.9	25 ±11	35		
S_f 21-35	11.3 ± 9.8	12.5 ± 7.1	15 ±12.9	18.8 ±10.5	11 ±5	35		
S_f 35-100	18.2 ±20.4	22.5 ±11.5	30.3 ±23.8	53.4 ±39.6	19 ± 9.7	90		
Total Cholesterol	196.1 ±75	203.1 ±55.5	223.3 ±50.5	259.4 ±75	215 ±80	275		

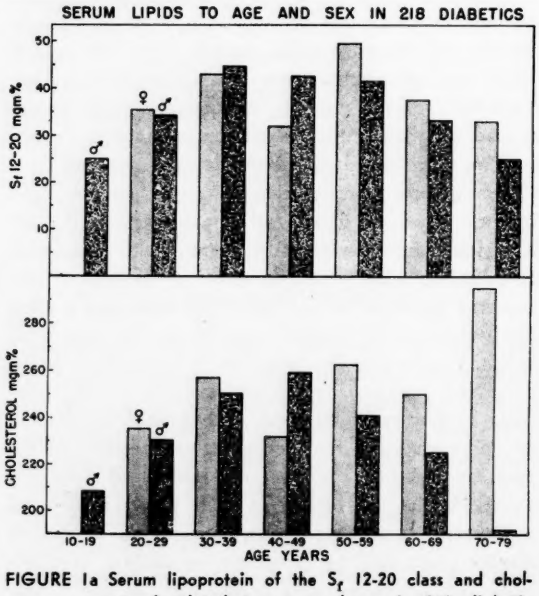

FIGURE 1a Serum lipoprotein of the S_f 12-20 class and cholesterol related to age and sex in 218 diabetic patients.

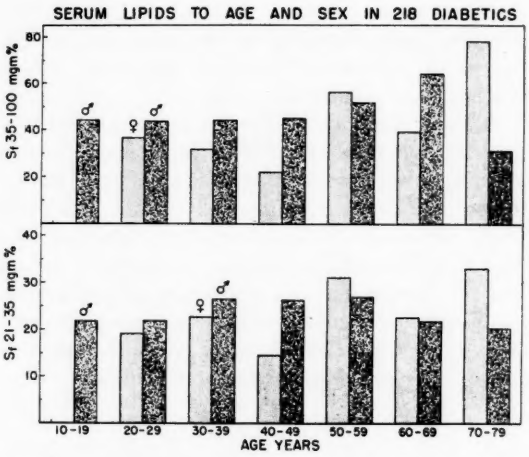

FIGURE 1b Serum lipoprotein of the S_f 21-35 and S_f 35-100 classes related to age and sex in 218 diabetic patients.

striking but in the S_f 21-35 and S_f 35-100 classes of lipoprotein there is persistent evidence that the lipid levels of the males exceed those of females. The relationship between insulin dose and serum lipids is described in Figure 2. The present data do not allow conclusions but there is evidence of some influence of increasing insulin requirement on the serum lipids, although the relationship is apparently not linear and not large. The explanation is especially complicated when it is recalled that it has been established that the degree of diabetic

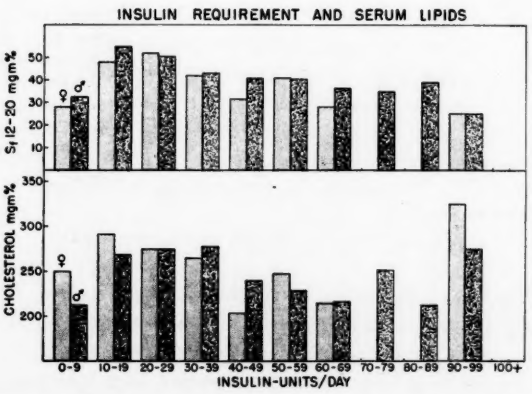

FIGURE 2 Serum lipoprotein of the S_f 12-20 class and cholesterol related to insulin dose in 218 diabetic patients.

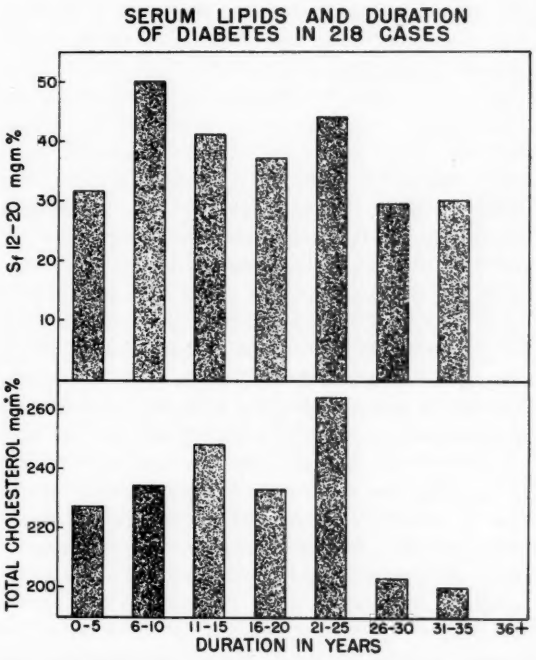

FIGURE 3 The relationship of the S_f 12-20 class of lipoprotein and cholesterol to the duration of diabetes in 218 patients.

control and the incidence of complications is not related to the size of the insulin dose.[4]

In Figure 3 are shown mean values for levels of cholesterol and the S_f 12-20 class of lipoproteins related to duration of diabetes. In the first 25 years of diabetes no definite changes in mean values appear. After 25 years a decrease in mean values, especially in the cholesterol is seen.

The relation between degree of control of diabetes and the distribution of mean lipoprotein and cholesterol values in the group of 144 patients is shown in Table 2. It will be seen that 96 of the total of 144 patients

TABLE 2 Mean lipoprotein and cholesterol values in 144 diabetic patients related to the degree of control of the disease.

Degree of Control	No.	S_f 12-20 mg%	S_f 21-35 mg%	S_f 35-100 mg%	Cholesterol mg%
Good	19	42(31)*	21(16)*	24(22)*	242(231)*
Fair	29	42	20	26	223
Poor	96	55	33	45	256

*One case of familial hypercholesterolemia excluded

were found to have maintained poor control. Twenty-nine had been under fair control and 19 were considered to have been under good control. The S_f 12-20 class of lipoproteins occurred with the same average concentration in the groups of good and fair control but the mean values were higher in patients with poor control of diabetes. A similar increase was shown in the concentration of the lipoproteins of the S_f 21-35 group and the lipoproteins of the S_f 35-100 group. The mean level of plasma cholesterol also was higher in the group with poor control although the difference in terms of percentage was not as great as shown in the levels of lipoproteins. Actually, the figures as given should be corrected for the fact that in the group of patients with good control is included one man, aged 31 years, whose value for lipoproteins of the S_f 12-20 class was 290 mg. per cent. This young man really was under good diabetic control but he suffered from familial hypercholesterolemia. If he is excluded, then the average for the remaining 18 cases under good control would fall to the values shown in parentheses in the tables (31 mg. per cent for the S_f 12-20 group, 16 mg. per cent for the S_f 21-35 and 22 mg. per cent for the S_f 35-100 lipoproteins and the mean cholesterol for that group would fall to 231 mg. per cent). In Figure 4 is shown the frequency distribution of the S_f 12-20 values in relation to good, fair and poor control. This figure serves to indicate the characteristic skewness of the distribution of the S_f 12-20 values. The same skewness is found for the other lipoprotein classes as well as for cholesterol. It is evident, however, that the frequency of high levels of S_f 12-20 values is greater with poorer control. This skewness characteristic of the data minimizes the usefulness of conventional statistical perimeters such as the mean and standard deviation.

It seems clear that a difference in the level of lipoproteins and of cholesterol exists in patients with poor control as contrasted with patients under good diabetic control. The basic and unresolved question is whether these differences in lipoprotein concentrations have etiologic importance in relation to control of the disease or whether they are a reflection of the differnce in incidence of complications in these groups. In other words, are these elevated values to be considered as cause or a consequence of the vascular disease?

DIABETIC NEPHROPATHY

In Figure 5 are contrasted the findings in 26 patients of the study group in whom diabetic nephropathy was present with 118 patients who were without evidence of kidney disease. In the nephropathy group only 4 cases were in the stage of terminal nitrogen retention. The mean value for the S_f 12-20 class of lipoproteins was 100 mg. per cent in the 26 patients with nephropathy and 39 mg. per cent in the 118 cases without nephropathy. For the S_f 21-35 class of lipoproteins the corresponding values were 62 and 21 mg. per cent, respectively. The mean cholesterol values were 318 mg. per cent for the nephropathy group and 234 mg. per cent for the 118 patients without renal disease. The difference between the two groups is striking. Thus in 118 patients without renal disease only 10 per cent had

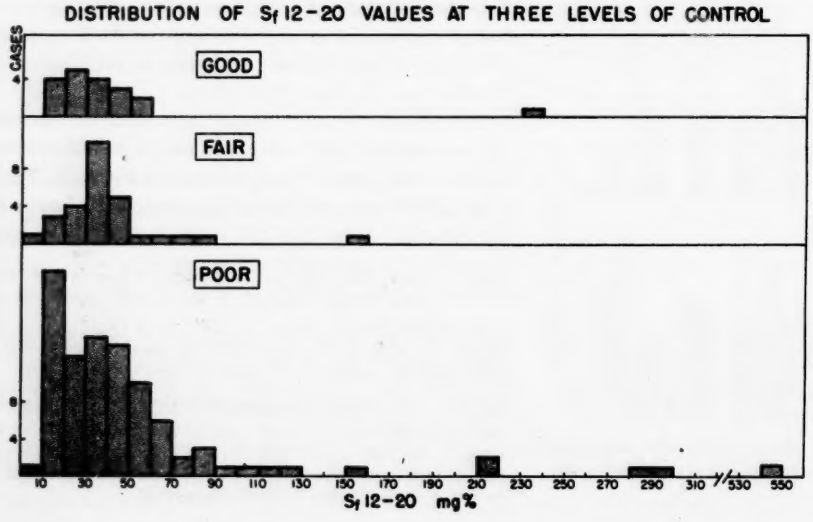

FIGURE 4 Frequency distribution of values for S_f 12-20 class of lipoprotein in 144 diabetics arranged according to degree of control.

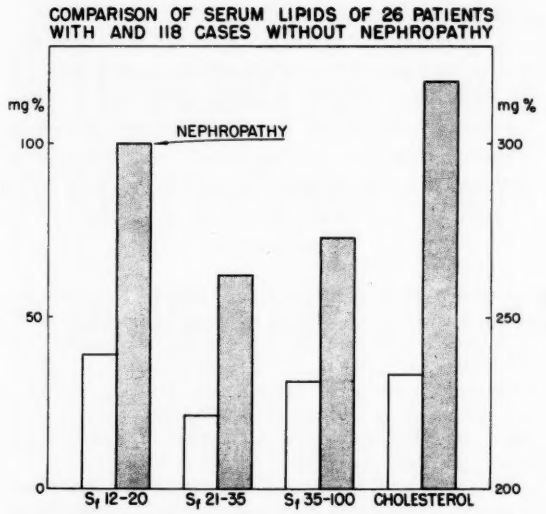

FIGURE 5 Mean serum lipid values in 26 patients with diabetic nephropathy compared with those in 118 diabetic patients without kidney disease.

values of the S_f 12-20 class of lipoproteins exceeding 70 mg. per cent but 31 per cent of the patients with nephropathy had values above this level. Similar differences appeared in the other lipid values. Fifty-eight per cent of the subjects with nephropathy had serum cholesterol values exceeding 260 mg. per cent, whereas only 24 per cent of the subjects without nephropathy had values above this level. In this group of patients the disturbance in protein metabolism with marked proteinuria and changes in the serum protein with an altered albumin-globulin ratio might be expected to lead to alterations in serum cholesterol and other lipids. Since disturbances of protein metabolism are an early sign of nephropathy[9] these serum lipids changes may be a consequence of the disease just as they seem to be in certain other diseases such as nephrosis.[10]

RETINITIS AND ARTERIAL CALCIFICATION

Two other clinical complications in this group of young diabetics are retinitis and arterial calcification. In order to show the relationship of these two complications to the serum lipid values, the patients have been divided into 4 groups. Group 1 includes patients with no or minimal retinal lesions and with no or minimal arterial calcification. Group 2 includes patients with the same

TABLE 3 The relationship of degrees of retinitis and arterial calcification to the mean lipoprotein and cholesterol values of 144 diabetics.*

Group	Number Cases	S_f 12-20	S_f 21-35	S_f 35-100	Cholesterol
			mg%		
1	49	31	15	23	217
2	19	37	13	24	247
3	33	63	43	52	259
4	43	69	41	53	274

*Group 1: no or minimal retinitis and no or minimal arterial calcification; Group 2: no or minimal retinitis but moderate to marked calcification; Group 3: moderate to marked retinitis but no or minimal calcification; Group 4: moderate to marked retinitis and moderate to marked calcification

minimal amount of retinitis but moderate to marked calcification of arteries. In Group 3 are included cases with moderate to marked retinitis but no or minimal calcification. Included in Group 4 are those patients with moderate to marked retinitis and also moderate to marked calcification of the arteries. The mean values for the various serum lipids measured are shown in Table 3. There is a progressive increase from Group 1 to 4 of all the values. However, a striking and characteristic feature of these changes appears in Figure 6 in which the values for the S_f 12-20 class of lipoproteins are placed beside the values for cholesterol in each of the four groups. It is apparent that the S_f 12-20 measurement is most characteristically associated with the increase in the degree of retinitis. The increase in cholesterol values are gradual throughout the four groups. The increase in the level of the S_f 12-20 class of lipoproteins is of much greater degree and seems to be characteristic and specific. The greater extent and

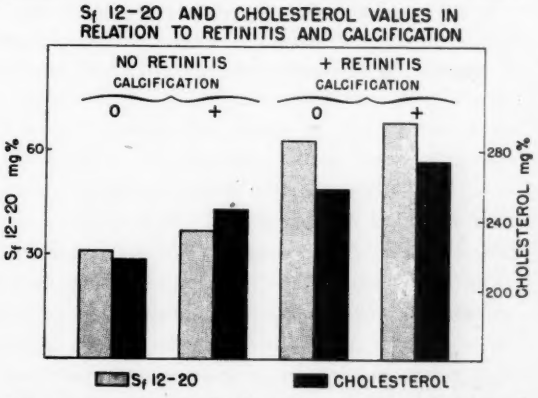

FIGURE 6 Comparison of the increase in S_f 12-20 class of lipoprotein and cholesterol values in 144 diabetic patients arranged according to presence or absence of retinitis and arterial calcification.

significance of the S_f 12-20 change illustrated in Figure 6 is emphasized by a consideration of the greater variability of the cholesterol measure. Since the standard deviation of cholesterol measurements is much larger (50-60 mg. per cent) it follows that mean differences must be large to be significant. Statistical treatment confirmed the finding that there is a significant difference between the S_f 12-20 values for patients with and without retinitis, whereas no significant difference could be found for the cholesterol values in these groups. Significance testing was done after a logarithmic transformation of the data for correction of skewness had been made.

SUMMARY

The serum cholesterol and lipoproteins of the S_f 12-20, S_f 21-35 and S_f 35-100 classes in 218 diabetic patients have been studied and compared with similar data obtained from 691 normal subjects.

It appears that the severity (as measured by insulin dosage) and the duration of diabetes are not important factors in determining the levels of serum lipoproteins and cholesterol in patients under treatment with insulin for periods up to 25 years.

The classification of 144 young patients with diabetes exceeding 10 years duration into 3 classes of control revealed higher mean levels of the serum lipids in the subjects with poor control. Levels of the S_f 12-20 lipoproteins exceeding 50 mg. per cent occurred in 32 per cent of patients with poor control, 17 per cent of patients with fair control and 10 per cent of patients with good control.

In 26 cases with diabetic nephropathy there was a marked elevation in all of the serum lipid components as compared with values obtained in the 118 subjects without renal disease.

A significant finding was the relationship between the presence of retinitis and elevated values of the S_f 12-20 lipoproteins. Arterial calcification showed a much less striking relationship to this lipoprotein. Statistical analysis reveals that the lipoprotein levels alone were significantly associated with retinitis.

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LIPOPROTEIN MOLECULES CHOLESTEROL and ATHEROSCLEROSIS in DIABETES MELLITUS*

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In the past, when the clinician discussed arteriosclerosis, he usually thought in terms of its more common form, which is characterized by hyperplasia of the medial layer of the artery. Clinically such vessels are easily palpated, they are thicker and harder than normal and a considerable proportion of them can be visualized with the x-ray, showing varying degrees of density and calcification. The vessels in this form of arteriosclerosis are not necessarily narrowed to a point at which they retard the flow of blood, and are not the common cause of gangrene of the extremities. In fact, this type of arteriosclerosis actually causes few symptoms unless or until a single organ, for one reason or another, becomes highly involved.

In the past it has been taken for granted, uncritically, that diabetes is the cause of this form of vascular disease in the diabetic. More careful analysis, however, has shown that arteriosclerosis involving the medial layer of the artery, frequently existed in the diabetic before the onset of his disease and that it evolves independently, irrespective of the diabetes.

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ATHEROSCLEROSIS

The topic which holds our main interest at this time presents quite a different picture. The vascular lesion with which we are concerned here is not the medial type of arteriosclerosis; it is a more specific lesion of the arteries which involves the intima, and it is known as atherosclerosis.

The pathologic physiology of atherosclerosis as it is understood today, evolves in the following manner. There is first, a period of hyperlipemia, brought about by ingestion of excessive amounts of fat, or an inability to metabolize the daily intake of fat in a normal way. After hyperlipemia has existed in the patient for a variable length of time, under certain unfavorable conditions, the arterial lesion is inaugurated.

It should be noted here that excess lipids occur in the blood of nondiabetics as well as in diabetics, and that atherosclerosis occurs in nondiabetics as well as in diabetics. But, atherosclerosis is far more common in diabetes than in other diseases. Briefly stated, it is assumed that a continuous or recurrent hyperlipemia leads to occurrence of abnormal deposition of fat into the intimal layer of the artery, and this is followed by calcium deposition. The x-ray reveals presence of calcium

deposits which in turn reveal the existence of atherosclerosis.

Such are the lesions found in the thoracic aorta and its branches including the coronaries, the abdominal aorta, the iliac arteries and the upper two-thirds of the femoral arteries. Below that, beginning in the popliteal area, the histologic picture in the diabetic seems to change. The atheromatous type of lesion seen in the aorta and its proximal branches is replaced by a process of fibrinization. A fibrinous hyperplasia of the intima occurs, even to the point of complete occlusion of the lumen. This is the type of lesion that leads to diabetic gangrene. This fibrinous type of lesion, in part at least, may be the product of certain hydrostatic factors. Klotz has shown many years ago, that arteriosclerosis can be induced by abnormal intravascular pressure. In the erect posture the intravascular pressures within the vessels of the leg, would tend to produce such lesions. During the past year Wilens has shown how intravascular pressures may cause fat infiltrations into the intima and media of arteries.[1]

Such are the lesions found at different levels in the arterial system in diabetes mellitus. They have been known and studied for 40 years, and it may be that the last words on the subject have not yet been said. It is not known which specific factor, if any in diabetes is responsible for the inauguration of these lesions, or how many other factors may be responsible for their occurrence. What is known is that atherosclerosis is a characteristic lesion in diabetes and that it occurs more frequently in diabetes than in other diseases.

Within the last few years Moreton called attention to the existence of certain types of chylomicrons in the circulating blood[2] and Gofman[3] delineated the existence of lipoprotein molecules of varying sizes in the blood of patients with coronary disease, hyptertension, diabetes mellitus, hypothyroidism, xanthosis etc.—those diseases in which atherosclerotic lesions are frequently found.

Aiming to cast additional light on the subject, under the auspices of the Committee on Lipoproteins of the Research Grants Division of the U. S. Public Health Service, we undertook the study of a thousand diabetics who had been under the care of one of us for one to 40 years, in the outpatient clinic and in private practice. The aim was to correlate the total clinical picture of the diabetic with the lipoprotein molecules, and cholesterol content of the blood.

The entire group was segregated into two parts, for comparative studies, on the assumption that private patients exercise better diabetic control, and that the findings in one group might, to a certain extent, differ from the other. We have been prescribing diets comparatively low in fat since the advent of insulin. We do not order more than 90 gm. of fat, usually 80 to 85 gm. of fat per day. At the same time we realize that it is all too common for patients to exceed the exact amounts of food ordered. It is equally true that if we ordered larger amounts of fat in the first place, our patients would take still more, and that would end in a relatively high fat diet.

This is a preliminary report, since about one third of the cases are still being processed; but to a large extent we are satisfied that the trends are already definitely established.

STANDARD VALUES

The Lipoprotein Committee of the Research Grants Division of the United States Public Health Service tentatively agreed on certain normal values for the lipoprotein molecules and cholesterol (the Kendall, Brodie, Abel method). These accepted values represent the findings in large groups in normal health and free of discoverable disease. Based on this experience, for the purposes of the present study, we consider that values for S_f 12-20 lipoproteins above 50 mg. per 100 cc., and for cholesterol higher than 250 mg. per 100 cc., are above normal. It is agreed that there can be no absolute point at which the normal ends and the abnormal begins. This is true of lipoprotein molecules, and of cholesterol values as well as of many other constituents in the chemistry or histopathology of the human organism.

PRESENT STUDY

Our first aim was to study the old question as to whether there is hyperlipemia in diabetes; and secondly, to what extent is hyperlipemia related to the destructive complications of diabetes mellitus.

Cholesterol Studies: We studied the cholesterol levels in relation to age, sex, race, private or clinic cases, underweight, overweight, blood pressure, size of heart, retinopathy, S_f 12-20 lipoprotein molecules, calcification in the arterial system as seen in the x-ray film, duration of diabetes and diabetic control. Our observations on retinopathy and other complications will be reported elsewhere.

Cholesterolemia in Diabetes: Figure 1 shows that in 614 cases of diabetes, the blood cholesterol was normal (under 250 mg.) in 255 and higher than normal in 359 cases. Thus high blood cholesterol occurred one

and one-half times as frequently as normal cholesterol. It will also be seen in Figure 1 that not only were there more cases of diabetes with high cholesterol, but that the average level of cholesterol was higher.

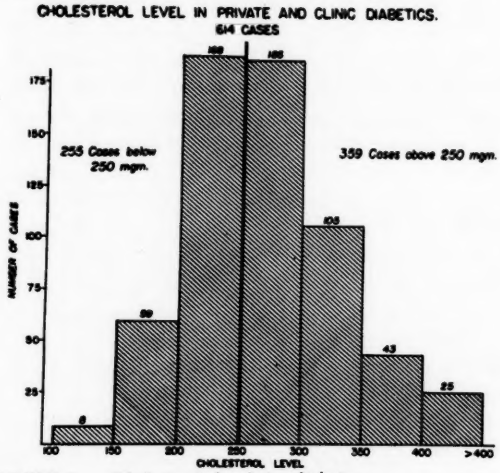

FIGURE 1 Cholesterol level in diabetes.

Cholesterol and Body Weight: Figure 2 shows that in a series of 531 cases of diabetes, the patients who were underweight showed low cholesterol values more frequently than those who were overweight. Elevated cholesterol occurred more frequently in those who were 25 to 75 pounds above normal. The greatest overweight was not accompanied by the highest cholesterol values. Evidently the fat that has been deposited under the skin is one thing and fat in the circulating blood is quite another. Thus a fat subject may show only a moderate cholesterol excess.

Cholesterol Levels in Diabetics with Hypertension: Among 626 cases of diabetes, hypertension was found in 33 per cent. This incidence of hypertension in diabetics corresponds to our previous studies. In this group of hypertensive diabetics, 20 per cent had high cholesterol value and 13 per cent had low cholesterol.Included in the hypertensive diabetics were 16 cases of Kimmelstiel-Wilson's disease; of these, 15 had high blood cholesterol values.

Heart Size and Cholesterol Levels: Is there a relationship between these two? In a series of 484 diabetics, heart measurements were checked according to the Groedel index and the Ungerlieder-Clark tables which are accepted standards. By these criteria, we found the size of the heart was normal in 57 per cent of the cases, larger than normal in 17 per cent and smaller than normal in 26 per cent. The finding of a small heart in 26 per cent of cases of diabetics was an arresting fact.

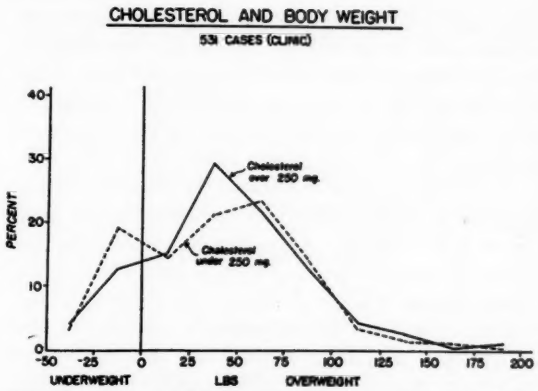

FIGURE 2 More diabetics 25-75 lbs. overweight have high cholesterol levels.

An analysis of the incidence of high blood cholesterol in these three groups revealed the following: In cases in which the heart was large, the cholesterol was low in 15 per cent and high in 25 per cent. In cases in which the heart was small, the cholesterol was low in 27 per cent and high in 33 per cent. In other words, the blood cholesterol was low in 42 per cent, cases in which the heart was abnormal in size, large or small, and high in 58 per cent of them.

To pursue this thought still further, it is an accepted fact that more than 80 per cent of diabetics are overweight at some time, before or after the onset of diabetes. Thus a diabetic who is overweight, and has a smaller than average normal heart, and who also has hyperlipemia, has a more or less complete background for cardiovascular complications. An obese diabetic with a small heart is as much handicapped as a Mack truck with an Austin motor.

Cholesterol and X-Ray Findings: As shown in Table 2, the following areas were examined. 1) thoracic aorta, particularly the aortic knob; 2) the abdominal aorta; 3) the femoral vessels and tibial vessels. In the 484 cases of diabetes examined, calcium deposits at one or more of the above mentioned areas were found in 295 cases; there was no positive evidences of calcification in 189 cases. In the 295 positive cases, 182, or 61 per cent, showed high blood cholesterol and 113, or 38 per cent, showed normal cholesterol. The inescapable conclusion is that where there is extensive calcification there is or there has been hypercholesterolemia.

On the other hand, in the cases in which no calcified vessels were detected by x-ray, 17 per cent showed cholesterol under 250 mg. and 18 per cent had cholesterol values over 250 mg. (Table 3). In the light of these findings it appears that there is a positive relation-

ship between hyperlipemia as manifested by hypercholesteremia, atherosclerosis, and calcium deposition. A blood cholesterol value above the normal level is the common finding in cases in which there is x-ray evidence of arterial calcification, and is an exceptional finding in patients who do not show calcification.

Cholesterol Level and Duration of Diabetes: It will be noted in Figure 3 based on 596 cases that the number of high cholesterol values increases during the first 15 to 17 years, which in reality is the period during which damage is accumulating in the diabetic. In separating clinic from private cases, it appears that this accumulation of damage extends over a longer period in private cases, in which diabetic control is better than clinic cases. After the 12th year in clinic cases and after the 17th year in private cases the incidence of high cholesterol drops off, because the total number of diabetics also diminishes as the patients advance in years, and as mortality takes its toll. Whatever the ultimate explanations may be, it is evident that hyperlipemia or hypercholesterolemia prevails during that time in the life of the diabetic in which we see the complications of the disease most frequently.

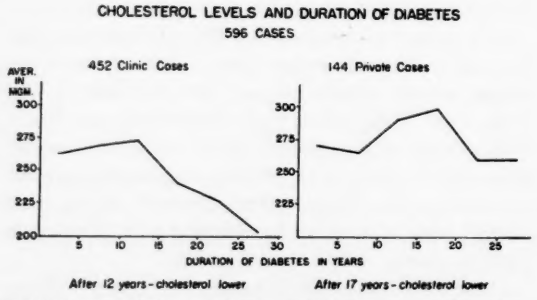

FIGURE 3 Cholesterol levels in diabetics, over the years.

LIPOPROTEIN STUDIES

We studied the S_f 12-20 lipoprotein molecules of the blood in relation to age, sex, color, occupation, duration of disease, body weight, blood pressure, size of heart, retinopathy, calcification of arteries, blood cholesterol value and diabetic control. According to Gofman, the S_f 12-20 lipoproteins contain 25 per cent of cholesterol and the question arises as to whether lipoprotein readings reflect the total blood cholesterol and whether cholesterol readings reflect the amount of lipoproteins in the circulating blood. On this point we will present our own observations later.

Sex and Color: In our previous studies as well as in this one, we find more female diabetics than males.

TABLE 1 Incidence of normal and abnormal sized hearts and cholesterol levels in each group

Heart Size and Cholesterol Level
Diabetes — 484 Cases

Large Hearts — 17%
Small Hearts — 26%
Average Size — 57%

Low Cholesterol with Large Hearts 15% with Small Hearts 27%
High Cholesterol with Large Hearts 25% with Small Hearts 33%

TABLE 2 Extensive calcification—high cholesterol
484 Diabetics — 295 Positive X-Rays
Calcified Vessels

Areas Involved	Cholesterol Normal	Cholesterol High
4	20.....6%	33.....11%
3	18.....6%	43.....14%
2	31.....10%	61.....20%
1	44.....15%	45.....11%
	113 Normal	182 High

TABLE 3 Cholesterol values in diabetics showing no calcification of vessels.

Cholesterol in 484 Negative X-Ray Cases
Cholesterol under 250 mg. 17%
Cholesterol over 250 mg. 18%

TABLE 4 S_f 12-20 lipoprotein values according to color and sex

Males	216	33%
Females	402	66%
Combined white and negro males		33% high S_f
Combined white and negro females		43% high S_f
White males		34% high S_f
White females		49% high S_f

Thus in 618 cases of diabetes there were 33 per cent males and 66 per cent females. The lipoprotein measurements revealed that 43 per cent of the female diabetics and 33 per cent of the males had S_f 12-20 lipoproteins higher than normal. In the white diabetics our figures show an increase in 49 per cent of females and 34 per cent of males. This difference is of no apparent significance.

Comparison of Private and Clinic Cases: In the same group of 618 cases, of which 23 per cent were private cases with better control on the average, a high value for S_f 12-20 lipoprotein was found in 26 per cent of the private cases and in 30 per cent of the clinic cases.

Overweight in Diabetes and S_f 12-20 Lipoproteins: An analysis of 626 cases of diabetes with overweight showed, first of all, that 40 per cent had high S_f 12-20 lipoprotein values and therefore hyperlimemia. It will be noted in Table 5 that the degree of obesity as reflected in the number of pounds overweight is not related to the occurrence of high S_f 12-20 lipoproteins. These values for blood lipids are related to circulating fat molecules in the blood, and not the stored fat in

the body of the individual. Whether the patient is 25 lbs. or 125 lbs. overweight does not mean that he will have a normal or high lipoprotein level at all times.

Lipoproteins in Hypertension: In 626 cases of diabetes, we found an existing hypertension in 34 per cent. In these hypertensives we noted that 41 per cent (90 cases) had high lipoprotein levels. Thus diabetes plus hyptertension, plus hyperlipemia, create a background for complications in the vascular system of the diabetic, and this triad therefore may be of diagnostic and prognostic significance.

Lipoproteins and Calcification of the Vascular System: Among 483 cases of diabetes we found in 297, calcified plaques as visualized by the x-ray in the thoracic aorta, abdominal aorta, femoral and tibial vessels. As Table 6 shows, there were 42 patients with calcification in all four areas—73 with calcification in 3 areas —86 with 2 areas and 96 with demonstrable plaques in only one area. In the entire group, 45 per cent of the cases showed high lipoproteins.

The table further shows that the number of diabetics who had calcifications in more areas in the arterial tree diminished as the number of areas involved increased. The trend here is interesting and lends itself to various interpretations. Hyperlipemia over a sufficient length of time, in the presence of a disturbed metabolism, or in the presence of other factors, leads to more extensive distribution of lesions, throughout the vascular system.

Lipoproteins and Heart Measurements: In 484 cases of diabetes the size of the heart was normal (43 per cent) in 266 cases (57 per cent). In 218 cases the heart was normal or average in size. Of these 218 cases, the suggest that abnormal heart size, plus hyperlipemia as indicated by both the cholesterol and lipoprotein values, heart was smaller than average in 60 per cent and larger than average normal in 40 per cent. Thus our figures showed one and one-half times as many small hearts as there were of large hearts in these cases of diabetes. They also show that in the small heart cases the S_f lipoprotein values were higher than normal in 35 per cent, while in the large hearts the lipoprotein values were higher than normal in 40 per cent of the cases. If we combine both the small and large heart cases into one group, we find that in 37.5 per cent of the cases in which the heart was abnormal, higher than normal lipoprotein levels were found. These findings may be potent factors in the causation of cardiovascular complications in the diabetic.

Lipoprotein Levels and Duration of Diabetes: Since it is generally true that most of the damage to the diabetic occurs during the first 15 years of his disease, it seemed worth while investigating the incidence of higher than normal levels of the lipoprotein molecules. This is shown in Table 8. Thus it appears that during the first 5 years, 29 per cent of 536 cases had higher than normal levels. During the 6 to 10 year period, 38 per cent and during the 11 to 15 year period, 44 per cent showed higher than normal lipoprotein levels. These analyses show that as the disease progresses, the high lipoprotein levels and therefore hyperlipemia occurs with greater frequency.

S_f 12-20 Lipoprotein Molecules and Diabetic Control: Our observations on this point cover a series of 531 patients who have been under our care from one to 40 years. Since the use of insulin, we have ordered a diet for them comparatively low in fat. We estimate the

TABLE 5 Increase in S_f 12-20 lipoprotein values with obesity.
626 Cases

Overweight		
0 to 25 lbs.	(53 cases)	41% High S_f
25 to 50 lbs.	(69 cases)	37% High S_f
50 to 75 lbs.	(60 cases)	41% High S_f
75 to 100 lbs.	(32 cases)	42% High S_f
100 to 125 lbs.	(9 cases)	39% High S_f

TABLE 6 S_f 12-20 lipoprotein molecules in positive x-ray cases
cases
Diabetes 483 Cases

Areas Involved	Cases	Normal S_f	High S_f	% - High S_f
4	42	26 cases	16 cases	37%
3	73	33 cases	40 cases	54%
2	86	50 cases	36 cases	41%
1	96	53 cases	43 cases	44%
Total	297	162	135	45%

TABLE 7 S_f 12-20 lipoprotein molecules as related to heart size.*
484 Diabetics

		Normal S_f	High S_f
Average Size	266 Cases		
Small Hearts	132 Cases	65%	35%
Large Hearts	86 Cases	60%	40%

1½ times as many small hearts as large in this series
37.5% of cases have high S_f

*(Groedel Index and Ungerleider-Clarks Tables)

TABLE 8 Incidence of high S_f 12-20 lipoprotein molecules as related to duration of the disease.
536 Cases

0- 5 years	29% High S_f
6-10 years	38% High S_f
11-15 years	44% High S_f

Longer duration—higher S_f levels

TABLE 9 Poor control showed greater incidence of high S_f 12-20 lipoprotein molecules in the blood of diabetics.

	531 Cases			
	Cases	Normal	High S_f	Per cent
Good Control	278	180	98	31%
Fair Control	109	65	44	40%
Poor Control	144	73	71	49%

TABLE 10 Cholesterol level is no index of the actual level of S_f 12-20 lipoprotein molecules in 40 per cent of the cases.

601 Cases of Diabetes

Low Cholesterol and Low S_f in same patient	170 =	359 Cases
High Cholesterol and High S_f in same patient		189
Low Cholesterol and Low S_f in same patient	53 =	242 Cases
High Cholesterol and Low S_f in same patient		189

Opposite trends in 242/601 = 40%

degree of diabetic control by the state of the patient over the years as shown in his continued history. We divided these cases into those that were under good control, fair control and poor control; on the basis of blood sugar, urine sugar, general health of the patient, etc. By these standards (Table 9) of those under good control, 31 per cent had high lipoprotein levels; of those under fair control, 40 per cent had high lipoprotein levels; and of those under poor control, 40 per cent had high lipoprotein levels. The trend here is a positive one, and the picture as a whole fits in with what we know about these patients and their disease in general, as well as the complications of their disease.

COMPARATIVE VALUES

Do the levels of cholesterol and S_f 12-20 lipoprotein molecules have the same clinical significance for the individual patient? Do they both tell the same story, and is the cholesterol reading interchangeable with the 12-20 lipoprotein molecule reading for clinical purposes? If that were true, much time and labor would be saved in the future. To that end we analyzed our findings in 601 cases with the following results:

In a series of 601 cases of diabetes, both the cholesterol and S_f 12-20 lipoprotein molecules were either above or below the normal levels in 359 cases; both showing a similar trend. But in the remaining 242 cases, the trends were in opposite directions. Either the cholesterol was low and the lipoprotein readings were high or the cholesterol was high and the lipoprotein levels low. In either case they were distinctly different and neither one could have been used for the other, for the purposes of clinical interpretation. Insofar as these observations go, we find an absence of similarity in trend in 40 per cent of the cases.

SUMMARY

We have made a preliminary survey of what is ultimately to be a series of one thousand cases diabetes. In this we are studying the S_f 12-20 lipoprotein molecules and the blood cholesterols in patients in relation to age, sex, color, occupation, duration of disease, overweight, size of heart, calcification of the thoracic and abdominal aorta, femoral and tibial vessels, blood pressure and diabetic control. We are also studying the retinopathies, diabetic lipodystrophies, and other phases and complications of this disease which will be reported in the completed studies in which we are now engaged. Up to the present time in our studies we have found that: 1) the frequency of hypercholesterolemia and increase in S_f 12-20 lipoprotein molecules, indicates that a diabetic has a constant tendency toward increased lipids in the blood stream: 2) that hyperlipemia is more common in those cases of diabetes in which appear the more extensive and more serious complications of the disease: 3) that where the cardiovascular system as reflected by abnormal heart size and calcification of arteries shows greater involvement, the incidence of hyperlipemia is highest. On all counts, there appears to be a distinct relationship between hyperlipemia and the various complications of this disease. The question of cholesterol readings in these cases serving as a substitute for the S_f 12-20 lipoprotein values was studied in a group of 601 cases of diabetes. We found that in 40 per cent of the cases the readings tended in opposite directions. While one was above normal level, the other was below in the same blood sample. In these, the level of one would not have indicated the actual value of the other.

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Ultracentrifugal Studies of Lipoproteins in Diabetic Sera*

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Previous reports by Gofman and associates[1-4] have indicated that a higher level of the ultracentrifugal S_f 12-20 fraction of serum lipoproteins is to be found in diabetic than in normal individuals. These data were obtained from populations of diabetic individuals which were not relatively homogeneous. They are also based upon the principle of computing the percentage of diabetics with values of S_f 12-20 below an arbitrary level. The method tends to obscure the fact that some diabetics exhibit very low concentrations as well as very high concentrations.

We have compared with normal individuals the more homogeneous groups of cooperating diabetics, uncooperating diabetics, and diabetics with some form of cardiovascular-renal disease. The data were treated so that the mean value of all the concentrations of S_f 12-20, both low and high for any group, would be considered.

The normal group consisted of 310 males between the ages of 26 and 60. All had blood pressures below 140 systolic and 90 diastolic; all electrocardiograms (made on nine-tenths of the individuals) proved to be normal. None had a history of diabetes, cardiovascular-renal disease or nephritis. Urinalysis showed absence of albumin and sugar. The cooperating diabetics, numbering 88 males, showed no evidence of cardiovascular-renal disease, were taking insulin as prescribed, had had diabetes for varying lengths of time, were on diets containing between 60 and 100 grams of fat each day and were judged to be good cooperators by their physicians.

The uncooperating diabetics, numbering 40 males, had no evidence of cardiovascular-renal disease but composed a somewhat heterogeneous group. They consisted of new patients, information about whose insulin and dietary intake was not accessible for evaluation, and patients whose physicians described them as poor cooperators. The cardiovascular-renal group, numbering 39 males, were diabetics who had had myocardial infarction, angina pectoris and hypertension in all possible combinations.

Carefully excluded from all groups were individuals

* Publication No. 16 of the Department of Biophysics.

diagnosed as having thyroid abnormalities, xanthelasma, alcoholism and other diseases known possibly to cause abnormal fat metabolism or for which medication might cause abnormal fat metabolism. Cases of Kimmelstiel-Wilson syndrome and epilepsy were also excluded.

Table I illustrates the mean values of S_f 12-20 lipoproteins for normal males in age groups from the third to sixth decades.

TABLE I S_f 12-20 Lipoproteins in Normal Males

	Age 21-30	Age 31-40	Age 41-50	Age 51-60
Number	76	131	78	25
Mean	36.4	39.5	46.2	35.8

Total Number	310
Mean of Means	40.1
Standard Deviation	22.1
Correlation coefficient (r)	.088, not significant .07
Correlation ratio squared (E^2)	.029, not significant .02

It may be seen that the mean of means for the 4 age groups is 40.1 mg. per cent which agrees very well with the findings of Jones, Gofman, et al[5] who found the mean concentration of S_f 12-20 lipoproteins to be 40 mg. per cent from 28 to 55 years.

It is noticeable that the fluctuation in our group means is greater than theirs, probably because of our use of smaller numbers. Our group means vary from 36.4 to 46.2 mg. per cent. However, the correlation coefficient of .088 means that there are more than 7 chances in 100 that there is no linear correlation between S_f 12-20 lipoproteins and the age groups. The correlation ratio squared, indicates that there are more than 2 chances in 100 that there is no association of any kind between S_f 12-20 and these age groups. Therefore, it becomes justifiable to combine the means of all the groups into a mean of means, 40.1 mg. per cent for comparison with the different groups of diabetics.

Table 2 gives a comparison of the lipoprotein values in the male groups of cooperating diabetics, cardiovascular-renal diabetics, and uncooperating diabetics from 26 to 85 years. The group of cooperating diabetics, numbering 88 individuals, was sufficiently large to be broken down into a 26-60 year sub-group and a 61 to 85 year sub-group. Since the means and standard deviations of the sub-groups remained unchanged, these diabetics may be compared with the normals of 21 to 60 years and with each other.

TABLE 2 S_f 12-20 Lipoprotein in Diabetic Males 26 to 85 years

	Co-operating Diabetics	Cardiovascular-renal Diabetics	Uncooperating Diabetics	Uncooperating Diabetics*
Number	88	39	40	38
Mean Value	40.2	41.4	65.6	46.7
Standard Deviation	27.3	21.1	88.4	27.9
Probability	1	.7	.08	.16

*Uncooperating Diabetics group omitting 2 cases in which values were over 350.

For S_f 12-20 lipoproteins it may be seen that the mean and the standard deviation of the cooperating diabetics does not differ from the normals or from the cardiovascular-renal diabetics. The mean for the uncooperating diabetics does appear to be higher, 65.6 mg. per cent. However, the four-fold increase in the standard deviation from 22.1 to 88.4 indicates that the uncooperating diabetics consist of a much more heterogeneous population than the other groups. Examination of the individuals in uncooperating diabetic group reveals the presence of two cases in which the S_f 12-20 values were extremely high—above 350 mg. per cent. When these are eliminated, it may be seen that the standard deviation and the mean for S_f 12-20 lipoproteins approaches that of the other groups. When we test the probabilities of differences existing between the diabetic groups and the normal group, it appears that there is practically no chance of a difference in S_f 12-20 lipoproteins between cooperating diabetics and the normal group, 7 chances out of 10 that there is no difference between cardiovascular-renal diabetics and normals, and 16 chances out of 100 that there is no difference between the uncooperating diabetics group (where two cases having values over 350 were omitted) and normals.

Therefore, our data, at this time, do not demonstrate a clear difference among any of these groups of diabetic males and normal males when both high and low values of S_f 12-20 are given equal weight in the analysis of the data.

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Degenerative Vascular Complications in Juvenile Diabetes Mellitus Treated with "Free Diet"*

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Before the discovery of insulin, vascular complications were seldom seen in juvenile diabetes mellitus. The disease picture was dominated by acidosis and coma, which in the majority of cases led to death before any signs of vascular disease had appeared. Even after insulin came into use, the combatting of acidosis and infection presented the main problem in diabetes therapy for about ten years. Increased knowledge of the use of insulin, the introduction of insulins with retarded action, the transition to a more normal calorie- and carbohydrate-rich diet, and modern chemotherapy brought about a rapid decline, however, in the frequency of coma and infections of diabetic children. The prognosis was considered much improved until the first alarming reports appeared of an increase in the frequency of vascular complications in diabetes of more than ten years' standing.

During the last decade a number of important papers have been published on this subject.[1-20] The most significant data from these earlier works have been collected in Table 1. Even with regard to differences in methods of examination, terminology, therapy, and presentation of the material, it is evident that with increasing duration of diabetes mellitus, vascular complications in the eyes, kidneys and peripheral arterial system are common, occuring in up to 70 per cent of cases after 15 years. These changes lead gradually to invalidism and death due to impairment of vision and to renal insufficiency. The cause of these complications is still unknown. It has been claimed, though, that they may be aggravated by so-called "unphysiological" control of diabetic patients: i.e. the treatment which permits a certain degree of hyperglycemia and glycosuria. As our experience from a series of Swedish diabetic children treated with free diet does not support this opinion, we have found it appropriate to present the results of a follow-up examination of these patients.

MATERIAL

This investigation includes 257 cases of diabetes in children with onset of diabetes before January 1st, 1950, and under the care of the Stockholm children's hospi-

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tals, the majority at the pediatric clinic of The Crown Princess Lovisa's Children's Hospital. Of these, 110 patients are still under regular control at the diabetes outpatient department of this hospital. Some are controlled at the other children's hospitals in Stockholm, while others live in the country and are under their local physician's control. Those remaining have been discharged from the children's hospitals because of age and are under control at diabetes outpatient departments for adults or by private physicians. We have sought contact with all by means of questionnaires sent to the patients and to their respective physicians. In this way we obtained information on all but 10 patients, whom we could not trace. Thereafter the patients were summoned for a follow-up examination. This included completion of the patient's history, a physical examination, a complete eye examination by the eye department of the Sabbatsberg Hospital,* x-ray examination of the lower extremities, tests for diuresis, glycosuria, acetonuria, and albuminuria, and determination of the blood sugar, non-protein nitrogen, and blood cholesterol. Unfortunately we were not able to give more than two-thirds of the patients such a complete examination. For the rest, only some of these tests could be performed.

The composition of the series is shown in Table 2. There was no difference in the sex distribution, 124 being boys and 123 girls. There were 17 deaths (7 boys, 10 girls), which makes a mortality rate of 6.9 percent. This mortality is similar to, or lower than, those of other comparable series (Table 1). Thus the mortality of White[4] in Boston was 11.8 percent, that of Rosenbusch[3] in Zurich 27.3 percent, that of John[21] in Cleveland 16.7 percent, and that of Selander[22] in Gothenburg 17.4 percent. There was no significant difference between the mortality rate in the whole material and in the four subgroups of different duration of diabetes.

The 17 deaths may be subdivided in five different groups with regard to the cause of death (Table 2). Three died of late vascular complications (renal or car-

*We wish to express our heartfelt gratitude for the careful study of our cases made by the physicians attached to this department.

TABLE 1 Review of the literature.

Author	Place	Year	Number of cases	Mortality %	Duration of diabetes (years)	Ocular complications: Stage I Retinal hemorrh. %	Stage II Retinal exudate %	Stage III Retinitis prolifer. %	Lesions of the lens %	Albuminuria Nephropathy %	Arteriosclerosis Vascular calcific. %	Hypertension %
O'Brien et al.	Iowa	1942	555		Not stated		4.1					
			260						13.8			
Eisele	Boston	1942	73		>20	42	32	2.7	16	15	30	20
							30.6					
					<1		10.7					
Wagener	Rochester	1945	1021		1-10		22					
					11-15		65					
					>20		73					
Rosenbusch	Zurich	1945	88	27.3			16.3		72.1	13.6		
White	Boston	1946	249	4.8	>20	65	50	8	1.6	35	70	40
			1901	11.8	0-30							
Mollerstrom	Stockholm	1047	2166		Not stated		5.1					
White et al.	Boston	1948	220		>20	75		16		40	70	55
Root	Boston	1948	154		>20						69	
			123	47	>15							
Chute	Toronto	1948	14		15-20	21	21		14	21	14	7
			13		>20	38	38		31	38	31	31
Croom et al.	Edinburgh	1949	60		>15		30			3	25	43
Jackson et al.	Iowa	1949	75		>10	36	9.3	1.3	14.6	4	16	4
			38		>15	50	15.8	2.6				
Dolger et al.	New York	1949	200		25		100			50		
Martensson	Lund	1949	219	21	>15		41			33	38	56
Engel	Falun	1950	185		0-23		16					
Wilson et al.[1]	Boston	1951	17		10-15		18[2]				17	
			20		15-20		40				30	
			36		20-34		36				44	
This investigation	Stockholm	1952	247	6.9	0-25	16	12.3	4.8	10	15.6	7.9	26
			33		>15	33.4	27.3	12.1		30.3	14.3	33

[1]Cases only with "controlled" treatment, "coma" and "free-diet" groups being excluded.
[2]These figures refer to "advanced" lesions, according to the authors.

TABLE 2 The composition of the material.

	Duration of Diabetes (years) on Jan. 1st, 1950 or at death					Mortality %
	0-4.5	5-9.5	10-14.5	> = 15	Total	
Living	60	73	57	40	230	
Deaths						
Vascular disease	—	—	1	2	3	1.2
Diabetic coma	2	2	—	—	4	1.6
Infections	3	—	2	1	6	2.4
Tuberculosis	—	—	1	1	2	0.8
Accidents	1	—	1	—	2	0.8
All	6	2	5	4	17	6.9
Total	66	75	62	44	247	

FIGURE 1

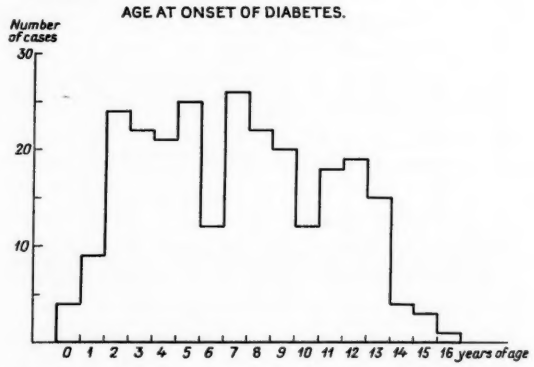
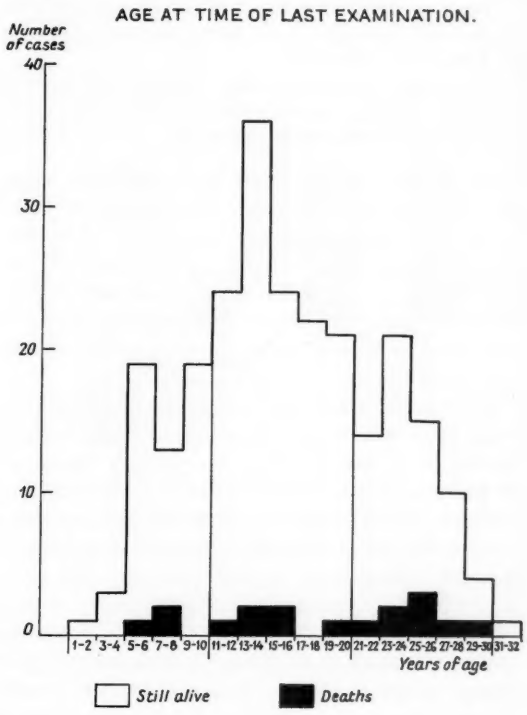


FIGURE 2



diac) after an average of 18 years of diabetes; four died in coma after a shorter period of diabetes—about five years; six died of non-specific infections, sepsis, pneumonia, pyelonephritis, brain abscess, scarlet fever; two died of tuberculosis. Four others had less severe tuberculosis. The frequency of tuberculosis in this material (2.4 percent) was similar to the Boston series of White.[4]

In Table 2 the duration of the disease is also illustrated. Sixty-six patients had had diabetes less than 5 years, 75 from 5 to 10 years, 62 from 10 to 15 years, and 44 more than 15 years. In the last group there were 6 patients who had had diabetes more than 20 years.

The age at onset of diabetes is shown in Figure 1. Between the ages of 2 and 13 years the frequency was fairly evenly distributed. In only 4 cases was the disease diagnosed in infants in the second half-year of life. Figure 2 shows the age distribution at the time of the follow-up examination or at death. The majority of the patients, 127, were between 10 and 20 years of age and 65 were over 20.

TREATMENT

All patients were treated according to the principles of diabetes treatment, which have been advocated by, among others, Stolte,[23] Soderling,[24] Lichtenstein,[25-30] Guest[31]: that is, controlled insulin treatment without dietary restrictions. Thus the patient is permitted a "free diet", which term implies "a normal diet corresponding completely with that of healthy children" (Lichtenstein[29]). A patient following this regimen is considered to be under good control when the following criteria are present:

1. A good general condition: normal vitality, normal height and weight, normal hunger and thirst, and absence of hypoglycemic symptoms.
2. A normal diuresis: patients are taught the normal values of diuresis and to record it at home occasionally.

3. Glycosuria is permitted but should not exceed 40 grams in 24 hours. In the majority of our cases, however, the amount of glucose in the urine seldom exceeded 10 to 20 grams in 24 hours.
4. Absence of ketonuria.
5. The fasting blood sugar value should preferably not exceed 200 mg. percent, although the 24-hour curve may show considerable variations.

The patients are seen at regular intervals, the length of which varies with the stage of the disease, the stability of the patient's metabolic state, his ability of satisfactory self-control, etc. During the first year of treatment the patient is seen about once a month; later on when the disease has become stabilized the patient is seen about once every second or third month, at least four times a year.

With careful, regular and continuous *control* in close cooperation with the patient and his family, a thorough knowledge is obtained about the patient's habits and his background from both a medical and socio-economic point of view. The patients are taught the importance of a regular way of living with regard to physical activity, sport, school work, sleeping hours, etc., but above all the necessity for regular mealtimes and a constant food intake is emphasized. By this means it is possible to avoid overfeeding and to see that the patients get a normal supply of calories. Mealtimes may be changed or small extra-meals inserted to counteract a tendency for insulin reactions. Excessive eating caused by hypoglycemia is treated by diminishing the insulin dosage. With regular weight control any tendency towards obesity is discovered early and treated with dietary restrictions—just as would be the case in a nondiabetic obese child.

Insulin is given according to the patient's need, that is, the amount of insulin necessary to get good control, as mentioned above. Careful regard is paid to the well-known variations in insulin requirements which occur at different stages of the disease, at different times of the year, during infections, in puberty, and during periods of increased physical activity or emotional instability, etc. The type of insulin treatment used by us is shown in Table 3. Amongst 213 cases, 178, (83.6 per cent) were controlled by one injection per day, while the remaining 35 patients (16.4 per cent) needed it twice. In most cases the original Hagedorn protamine insulin without zinc was found to give a better control with less reactions than protamine zinc insulin. In sev-

FIGURE 3

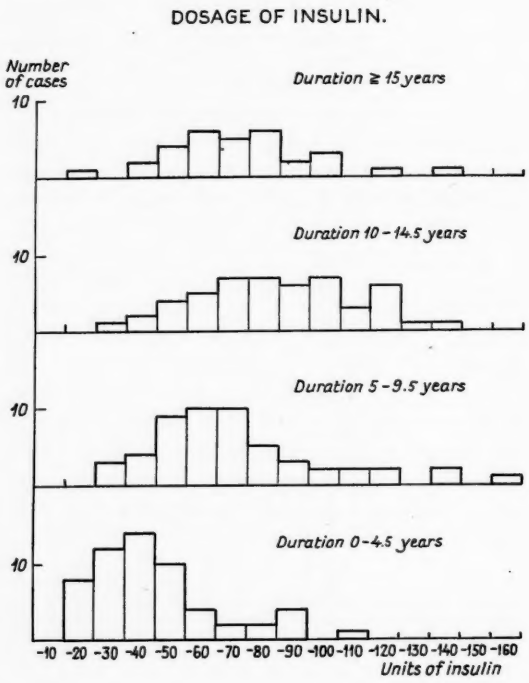


TABLE 3 Different types of insulin treatment.

KIND OF INSULIN	ONE INJECTION PER DAY Units of insulin per 24 hours								TWO INJECTIONS PER DAY Units of insulin per 24 hours							
	Less than 50		50-80		More than 80		Total		Less than 50		50-80		More than 80		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Protamine	62		27		7		96	53.9	—		3		1		4	11.4
Protamine zinc	5		14		2		21	11.8	—		3		1		4	11.4
Regular	—		—		—		—		3		5		5		13	37.1
Protamine + Regular	—		8		11		19	10.7	—		2		1		3	8.6
Protamine zinc + Regular	3		22		17		42	23.6	1		1		8		11	31.4
Total	70	39.3	71	39.9	37	20.8	178	100.0	4	11.4	14	40.0	17	48.6	35	100.0

eral cases a combination of long-acting and regular insulin was used. The average dosage of insulin is shown in Figure 3.

It will be seen from the above that this regimen of free dietary treatment of diabetes implies a strict control of the patients. We are anxious to emphasize this as some authors seem to regard patients following this type of treatment as comparable with those who "on their own volition" follow "a free-diet type of management, without regular examinations for sugar in the urine or blood" (Wilson and others[20]). We consider such a conception entirely erroneous. *Free diet does not mean freedom from control,* according to our standards.

RESULTS

OCULAR CHANGES. Diabetic changes have in our cases appeared in the eyes as diabetic retinopathy, diabetic cataract, and as the rare diabetic iris lesion, rubeosis iridis.

Diabetic retinopathy has been studied in detail by (among others) Ballantyne,[32] Wagener,[2] Hanum,[33] Waite and Beetham,[34] and Ashton.[35] According to these authors we have classified the cases of retinopathy in this material in three stages:

Stage 1: a) Capillary microaneurysms, the formation of which probably is the very earliest retinal change. They are located in the venous part of the capillaries. b) small hemorrhages, round or oval, located in the deeper layers of the retina.

Stage 2: Waxlike, ivory-colored, well-delineated exudates appear, small at first, but later coalescing. The hemorrhages become larger and increase in number.

Stage 3: Large superficial hemorrhages, sometimes penetrating into the vitreous formation of new vessels and proliferation of the connective tissue of the retina and considerable impairment of vision,—retinitis proliferans.

In the first two stages the patient's vision usually remains normal, and absence of subjective symptoms does not exclude the possibility of retinopathy.

The incidence of retinopathy in 187 of our cases is shown in Table 4 and Figure 4. The frequency of retinopathy increases as diabetes continues. After more than 15 years' duration, 72.7 percent had some form of retinopathy, although only 12.1 per cent of these were in Stage 3. In the whole series retinopathy was present in 33.2 per cent, and among these 4.8 per cent had reached Stage 3. As is evident from Table 1, the same high frequency of retinopathy may be found in the diet-treated series reported by White,[4] White and Waskow,[5, 6] Chute,[8, 9] Dolger,[12-14] Wagener,[2] and others. A comparison with the recent study of Wilson and others[20] is more difficult, as these authors only distinguish between "minimal" and "advanced" retinal lesions. If one regards, however, the Stages 2 and 3 of our classification as representing together advanced lesions, 39.4 per cent of our cases with a duration of diabetes more than 15 years will belong to this group. This figure may be compared to the figure in the paper of Wilson and others[20] which indicates the incidence of "advanced" retinopathy in the group of "controlled" patients with a duration of diabetes of 15 to 20 years. This figure is 40 per cent, which is identical with the corresponding figure in our

FIGURE 4

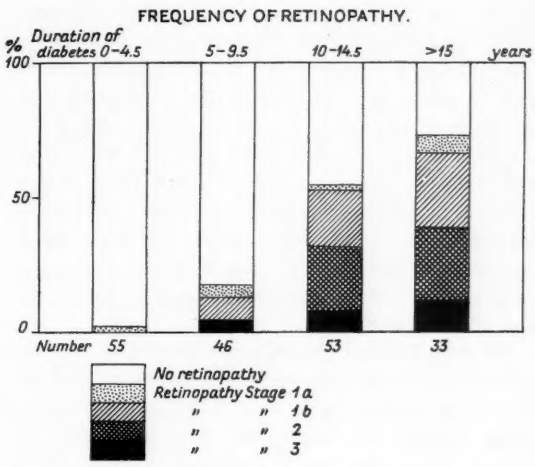


TABLE 4 Frequency of retinopathy

Years since onset of diabetes	None		Stage 1a		Stage 1b		Stage 2		Stage 3		All retinopathies		Total No.
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
> = 15	9	27,3	2	6,1	9	27,3	9	27,3	4	12,1	24	72,7	33
10-14,5	24	45,3	1	1,9	11	20,8	13	24,5	4	7,5	29	54,7	53
5-9,5	38	82,6	2	4,4	4	8,7	1	2,2	1	2,2	8	17,4	46
0-4,5	54	98,2	1	1,8	—		—		—		1	1,8	55
Total	125	66,8	6	3,2	24	12,8	23	12,3	9	4,8	62	33,2	187

series of patients, who were not given a measured diet.

A lower frequency of retinopathy has been given by Croom and Scott,[10] Jackson and others,[11] Martensson[15-17] and Engel.[18] Thus, in the group of Jackson and others,[11] among 38 cases with duration of diabetes more than 15 years, there was retinopathy in 68.9 per cent. Although in only 18.4 per cent were the lesions advanced, and in only one case (2.6 per cent) had Stage 3 been reached. A low incidence of retinopathy is also reported by O'Brien and Allen[36] (4.1 per cent) and by Mollerstrom[37] (5.1 per cent). In the two latter papers no statement was made, however, as to the duration of diabetes in the series, from which these frequency figures were calculated.

We were unable to establish any connection between the severity of the disease, judged on the basis of the size of the insulin dosage, and the frequency of retinopathy (Figure 5). When there was retinopathy the average insulin dose was 71 units and in cases without retinopathy 60 units per 24 hours, but this difference is obviously due to the fact that the last-mentioned group contained those cases with a duration of diabetes less than 5 years, in which group the average insulin dose was smaller than in the rest of the material (Figure 3).

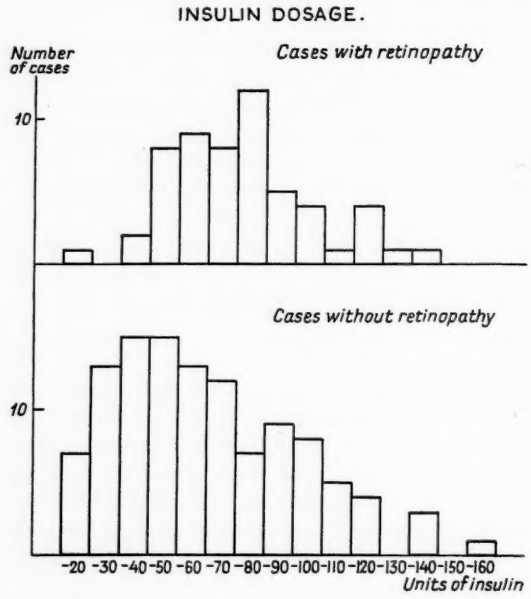
Diabetic lens changes were found as a slight cloudiness of the lens in 10 per cent of our cases but this had not given rise to any subjective symptoms. This figure is similar to the figures of other investigators except Rosenb ısch,[3] in whose series 72.1 per cent of the cases had a special lens lesion called Verdichtung der Abspaltungszonen, a cloudiness in the first discontinuity surface, recognizable only upon examination with a slit lamp. As far as we know no other worker has noted this phenomenon.

Rubeosis iridis was found in only one case, a woman who had had diabetes for 17 years and who also had severe retinitis proliferans. She died of tuberculosis at the age of 21.

DIABETIC NEPHROPATHY. The extent to which intercapillary glomerulosclerosis, described, among others, by Kimmelstiel and Wilson,[38] Goodof,[39] Mann and others,[40] is a specifically diabetic kidney lesion has been much discussed. It is more frequent in diabetes than in other conditions, but it also occurs occasionally in hypertension and glomerulonephritis, though seldom in advanced form (Kimmelstiel and Porter,[41] Henderson and others,[42] Bergstrand and Bergstrand[43]). It was found at autopsy in two of the three cases dying from renal failure.

The clinical manifestations of diabetic nephropathy

FIGURE 5



are variable. In the majority of our cases the first sign appeared after at least 10 years of diabetes in the form of albuminuria, at first sporadic, later constant, though quantitatively insignificant. In spite of this, the patient may be subjectively free of symptoms for years. Only exceptionally could signs of urinary infection be observed. Renal insufficiency, with hypoproteinemia, edema, hypertension, and uremia did not appear until the terminal stage. We have not seen the type of nephropathy which has been described by Fanconi and others,[44] who with a diet rich in fruits, vegetables and fats, but poor in protein, got a high incidence of severe nephropathy with hypoproteinemia and hypercholesterolemia.

The frequency of albuminuria in our material is shown in Table 5. In the whole series it was 15.6 per cent and in the group of cases where the duration of

TABLE 5 Frequency of albuminuria.

Years since onset of diabetes	None		Present		Total
	No.	%	No.	%	No.
≥ 15	23	69,7	10	30,3	33
10-15	32	66,6	16	33,3	48
5-10	45	95,7	2	4,3	47
0- 5	57	98,3	1	1,7	58
Total	157	84,4	29	15,6	186

diabetes was more than 15 years it was 30.3 per cent. Albuminuria, like retinopathy was thus more common when the disease had persisted for a long time. Albuminuria was in most cases the only sign of kidney disease. The frequency of albuminuria in our material is equal to that of other similar series (Table 1).

ARTERIOSCLEROSIS. Good methods of diagnosing arteriosclerosis at an early stage are still lacking. X-ray examination of the lower extremities in order to demonstrate vascular calcification is the simplest and most widely used method, but it gives positive results only when the lesions are advanced. Other methods, such as oscillometry, measurement of the skin temperature, or analysis of the pulse wave have also failed to make early diagnosis possible. Nor has the diagnostic significance of increased blood lipids been satisfactorily clarified.

In our material vascular calcification was diagnosed either by direct examination at autopsy or in life by x-ray. It was found in 9 out of 114 cases (7.9 per cent.) These nine cases had all had diabetes for more than 10 years. Among those who had had the disease over 15 years the frequency of arteriosclerosis was 14.3 per cent (Table 6). Chute[8,9] and Jackson[11] found a similar incidence of arteriosclerosis, but in the groups of White,[4] White and Waskow,[5,6] Root,[7] Croom and Scott,[10] Martensson,[15-17] and Wilson and others[20] it was much higher, 25 to 70 per cent.

TABLE 6 Frequency of peripheral arteriosclerosis.

Years since onset of diabetes	None No.	%	Present No.	%	Total No.
≧ 15	24	85,7	4	14,3	28
10-15	35	87,5	5	12,5	40
5-10	22	100,0	—		22
0- 5	24	100,0	—		24
Total	105	92,1	9	7,9	114

TABLE 8 The cholesterol level of the blood.

Years since onset of diabetes		Cholesterol level of the blood Mg. per cent <150	150-250	251-350	>350	Total number
≧ 15	Number	1	15	7	3	
	Per Cent	62		38		26
10-15	Number	7	26	8	5	
	Per Cent	72		28		46
5-10	Number	12	40	2	3	
	Per Cent	91		9		57
0- 15	Number	3	25	8	1	
	Per Cent	76		24		37
Fresh untreated cases	Number	1	25	9	3	
	Per Cent	68		32		38
	Number	24	131	34	15	
Total	Per Cent	76		24		204

Hypertension (a systolic blood pressure of over 140 mm. Hg. and a diastolic of over 90 mm. Hg.) was found in about 26 per cent, as is shown in Table 7. However, since most of the blood pressure determinations were carried out at the outpatient department on ambulant patients, the actual hypertension frequency was probably lower. In only six cases (4.0 per cent) was the systolic blood pressure higher than 170 mm. Hg. and in two cases (1.3 per cent) the diastolic pressure was over 110 mm. Hg.

The cholesterol content of the blood was determined in 204 cases. The result is shown in Table 8. Values of over 250 mg. per 100 cc. were found in 24 per cent. Hypercholesterolemia was most common among those who had had diabetes for more than 15 years.

As regards the relationship between the different types of complications we were only able to observe a

TABLE 7 Frequency of hypertension.

Years since onset of diabetes	Systolic blood pressure mm. Hg. <140 No.	%	140-170 No.	%	>170 No.	%	Diastolic blood pressure mm. Hg. <90 No.	%	90-110 No.	%	>110 No.	%	Total number
≧ 15	20	69	7	24	2	7	19	66	9	31	1	3	29
10-15	36	72	12	24	2	4	30	60	20	40	—	—	50
5-10	30	75	8	20	2	5	30	75	9	23	1	2	40
0- 5	27	90	3	10	—	—	28	93	2	7	—	—	30
Total	113	76	30	20	6	4	107	72	40	27	2	1	149

regular connection between albuminuria and retinopathy, in that the majority of the cases with albuminuria, 99 per cent, had retinopathy. On the other hand, only 44 per cent of the cases with retinopathy had albuminuria.

We found no difference in the sexes' susceptibility to complications except in one respect: of the 9 cases with retinitis proliferans, 7 were female. In Hanum's[33] series of 183 cases of retinitis there was a similar preponderance of females.

There have been only a few nonvascular complications, such as retarded growth, hepatomegaly, lipomatosis, etc., in this series, and no case of diabetic neuropathy. Lichtenstein[25-30] reported on these in earlier articles and they will not be discussed here.

COMMENT

The results of our investigation show an increasing incidence of degenerative vascular complications in long-standing juvenile diabetes mellitus treated without dietary restrictions but otherwise under regular control. From our figures it is evident, however, that the frequency of these complications was not higher than among patients treated with measured diets (Table 1). Joslin, [45-47] Wilson et al.,[19, 20] and others have asserted that the vascular complications of diabetes are aggravated by persistent unphysiological hyperglycemia and glycosuria such as are found particularly in connection with treatment without dietary restrictions. However, when comparing their results of diet-treated cases with ours, no evidence is obtained in support of this view. On the contrary, at Joslin's own clinic (White[4-6]) the frequency of complications is as high as in our series and, in fact, his patients have had radiologically demonstrable arteriosclerosis more frequently than ours. In the cases of Wilson and others[19, 20] the frequency of retinopathy and vascular calcification is also similar to ours, even in their best controlled group. Among those cases in Wilson's material who had poor control, the incidence of ocular, renal and vascular complications is evidently much higher but, as has been pointed out before, such patients are by no means comparable with our cases. Their patients, who maintained a "poor" or "fair" control were "living on an unmeasured diet without constant use of insulin and without constant control of glycosuria". Neither do we consider such control adequate. Although we do not consider that a measured diet is necessary for the diabetic child, we do believe that a sufficient amount of insulin should be given continuously and that the degree of glycosuria and the patient's general condition should be regularly controlled as indicated earlier. We are also convinced that the omission of *that* control will increase the risk of complications.

In this material the degree of supervision has been variable, as it is in all groups of diabetic patients, and some of the patients have come short of our criteria for good control. This is especially true as regards patients living in the country where distances make regular attendance more difficult and among patients from the lower socio-economic classes. Unfortunately it has not been possible to make a fair division between patients with good and poor control. This is partly due to the difficulty of accurately estimating its degree in ambulant patients, where there are no continuous records of diuresis, glycosuria, blood sugar, etc. Thus we do not know if there was any correlation in our material between the degree of control, according to our criteria, and the incidence of complications.

The problem of the degenerative vascular complications in diabetes is not settled by the factor of control alone. In many series of diabetics, occasional cases of long-standing diabetes are met with in which there has been good control and still development of marked vascular lesions appeared; conversely, in cases with poor control few or no complications may be seen. Dolger[12] has described illustrative cases. Obviously there are still unknown factors in the etiology of diabetic complications.

Our experience with this group of diabetic children treated without dietary restrictions, and the comparisons made between this group and diet-treated series, have led us to the conclusion that the use of measured diets does not protect the patients against degenerative vascular complications to a greater extent than treatment with a free and normal diet, combined with adequate insulin therapy and regular supervision. Since, furthermore, a free diet offers diabetic children a chance to lead a happier, more natural and normal life, we consider it preferable to treatment with measured diets.

SUMMARY

A survey is given of the incidence (in previous reports) of degenerative vascular complications in long-standing juvenile diabetes mellitus, (Table 1).

The results of a follow-up examination of 247 cases of diabetes mellitus beginning in childhood is given. All were treated according to the principles described previously, i.e. controlled insulin treatment without dietary restrictions. The criteria for good control under this type of treatment are described, and the importance of regular supervision is emphasized.

The mortality rate was 6.9 per cent. The deaths are analyzed.

Diabetic retinopathy is classified in three different stages. The incidence of retinopathy in 187 cases is given in Table 4 and Figure 4. The frequency of retinopathy was correlated to the duration of the disease. After more than 15 years' duration of diabetes 12.1 per cent had reached the stage of proliferative retinitis.

The occurrence of diabetic nephropathy is given and its symptomatology in these cases described. After more than 15 years of diabetes, 30.3 per cent had albuminuria.

The incidence of vascular calcification in the legs was low when compared with the results of other authors. After 15 years of diabetes, it was found in 14.3 per cent.

The results are compared with those of other authors, using measured diets. It is shown that in general the frequency of vascular lesions was the same in this group, as in the diet-treated cases, except as regards vascular calcification, the incidence of which was lower than in most other series.

The conclusion is made that the use of measured diets does not protect diabetic children against degenerative vascular complications to a greater extent than treatment with a free and normal diet, when combined with an adequate insulin therapy and a regular and continuous control. This form of treatment is consequently considered preferable because of its obvious advantages in offering the diabetic children a chance of a more natural and normal life.

The problem of degenerative vascular complications in diabetes is not a problem of control alone. There must be other, still unknown etiologic factors, inherent in the disease itself.

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A PROPOSED "CHARTER OF ANIMAL RIGHTS"

The World Federation for the Protection of Animals, representing humane societies in twenty-five countries, met recently in the Netherlands to start a push for an international "charter of animal rights."

The proposed law does not provide for a ban on animal experimentation, but would ask that such investigations be allowed only by special government permission "if there is every possible guarantee that no needless suffering be inflicted" and that "higher grades of animals, such as horses, dogs, monkeys and cats" should be "as far as possible precluded from vivisection."

——*From the* Bulletin of the National Society for Medical Research

ABSTRACTS

ALSLEV, JENS (*Med. Clin., Univ. of Kiel, Germany*): Comparative studies on intermediary galactose and dextrose metabolism in healthy and diabetic individuals. Klinische Wochenscrift 30:406-07, May 1, 1952.

The difference in pyroracemic acid and lactic acid curves following galactose and dextrose administration in normal individuals allows the conclusion that in some respects the breakdown of galactose is different from that of glucose. The similarity in galactose, pyroracemic acid, and lactic acid curves following galactose administration in normal and diabetic individuals permits the conclusion that galactose breakdown occurs in diabetics in the same manner as it does in healthy subjects. The typical disturbance in glucose metabolism of diabetics is not present in their galactose metabolism.

ANNOTATIONS (*England*): Diabetes and stress. Lancet 1:959-60, May 10, 1952.

Good diabetic control is usually described in terms of accurate adjustment of insulin dosage to a regular prescribed diet. However, even with a carefully devised regimen, the severity of the diabetes may fluctuate widely, so that the condition remains grossly unbalanced. Such changing insulin requirements are commonly associated by the patients themselves with domestic upheaval, strained circumstances at work, or other worry; and this aspect has been studied at several large diabetic clinics. Hinkle and Wolf at the New York Hospital, investigated the effect of stress and anxiety on metabolic changes in normal and diabetic patients. They found that in the fasting normal person at rest there was initially little change in the blood sugar and ketone concentrations or rate of urine output; but later in the fast day the blood sugar fell slowly to 40 to 50 mg. per 100 ml. and the blood ketone concentration rose. At about the same time there was moderate diuresis. Similar changes took place in normal people in stressful situations without starvation. Hinkle and Wolf carefully avoid implying that the emotions occasioned by the stress caused these metabolic changes; but they did notice a correlation between anxiety and diuresis and between anger, dejection, resentment, or loneliness and a rise in blood ketones.

In diabetics, the metabolic response to psychological stresses was similar but often greater. Moreover "stress diuresis" associated with anxiety may be induced in diabetics whether or not they have glycosuria. On the other hand, under basal conditions, up to 7 per cent glucose can be passed in the urine without polyuria. The usual initial reaction of a fasting diabetic to a stress situation was a transient fall in blood sugar, occasionally great enough to cause hypoglycemic symptoms, and an increase in blood ketones. If the stress persisted, the blood sugar was likely to rise, especially when fear and anger were prominent features of the emotional response. Carbohydrate tolerance was also found to be affected by stress. Circumstances associated with resentment or sadness tended to accentuate the diabetic type of glucose tolerance curve, whereas with less stress or with anxiety the sugar tolerance was not so impaired. Diabetics with initially high blood sugar levels reacted to conflicts by a rapid rise in blood ketones and greatly increased secretion of water, glucose, ketones, chlorides,

and fixed base. In this way the metabolic changes typical of diabetic ketosis can develop rapidly; in fact, episodes of diabetic ketosis are often connected with stressful situations. Diabetes, when it first presents itself, commonly does so in a setting of stress, such as a reverse in business or loss of a near relative. At the time of the flying bombs such stress reactions were very evident in London diabetic clinics, A near miss from a flying bomb might score a direct hit on the diabetes, which would temporarily require greatly increased doses of insulin. Such factors should not be forgotten in the less dramatic conditions of peace, for helpful general advice and understanding can do much to lessen the fluctuations in the disease.

ANONYMOUS: Diet and insulin effect on diabetes and cataract development in rats. Nutrition Rev. 10:147-48, May 1952.

The factors involved in the development of the complications of diabetes are still poorly understood. Cataracts, renal lesions, and, in lesser incidence, vascular lesions have been described in the experimental animal made diabetic by alloxan or by pancreatectomy. The influence of dietary constituents and control of hyperglycemia by insulin on the development of these complications has been the subject of investigation in numerous studies. However, species variations have prevented the formation of broad conclusions. A recent attempt to delineate the relative influence of carbohydrate, protein, and fat and the control of hyperglycemia on the appearance of cataracts in the diabetic rat has been reported. The evidence offered is suggestive of the effect of protein in protecting experimental animals against the development of diabetes. The degree of glycosuria and the frequency of cataract development also appear to be correlated. The unquestioned acceptance of the hypothesis of hyperglycemia as a primary cause of cataract development, however, will await extension of this type of study.

ARTETA, J. L. (*Inst. of Exper. Endocrinol., Madrid*): Kidney and alloxan: Researches on their role in the production of alloxanic diabetes. Acta physiologica latinoamericana 2:65-72, March 1952.

In 1946, Jiménez Diaz, Grande, and Oya showed that the temporary circulatory exclusion of the kidney by clamping off its vascular pedicle during the injection of alloxan prevented the development of the severe diabetes which, together with the uremic syndrome, is the usual consequence of the injection of the doses employed (80 to 100 mg. per kgm. of body weight). The authors assumed that such a protection could be due either to the necessity of contact of the alloxan with the kidney in order to develop its diabetogenic action or to the existence of a renal injury caused by the alloxan, which would condition its diabetogenic effects. The injection of alloxan in the renal artery of dogs, with prior clamping of the vascular pedicle of the opposite kidney, produced a severe renal injury (in 4 dogs out of 5 which were autopsied); however, the animals did not become diabetic. The clamping of the hepatic pedicle also protected the dogs against the diabetogenic action of a high dose of alloxan. The clamping of the renal pedicles caused circulatory changes in the pancreas. It has been proved, through injection of India ink in a 50 per cent water solution, that the dyeing in the pancreas of the animals with clamped kidneys was less intense and more irregular than in control animals. The existence of a renal injury provoked by alloxan is not necessary for the development of alloxanic diabetes. The protection resulting from the temporary circulatory exclusion of the kidneys is not due to lack of renal injury but is a consequence of a reflex action on the pancreatic circulation.

AZERAD, E.; AND NATAF, J. (*Brussels*): Treatment of severe acidosis in diabetics. La vie medicale internationale 1:6, April 23, 1952.

Some considerations concerning the treatment of severe decompensated acidosis in the diabetic are presented. It is pointed out that in view of the difference of opinion among specialists, no fixed rules can be established to be followed blindly. Speed of action is emphasized as being of prime importance, since the disequilibrium in diabetic acidosis becomes increasingly severe as time elapses.

BACCHUS, HABEEB; HEIFFER, MELVIN H.; AND ALTSZULER, NORMAN (*George Washington Univ. Sch. of Med., Washington, D.C.*): Potentiating effect of ascorbic acid on cortisone-induced gluconeogenesis. Proc. Soc. Exper. Biol. & Med., 79:648-50, April 1952.

The action of ascorbic acid treatment on the gluconeo-

genic action of cortisone was investigated in adrenalectomized mice. The deposition of glycogen in the liver is enhanced in animals treated with ascorbic acid in addition to cortisone. This observation is discussed in relation to the action of the vitamin in preventing the activation of the pituitary-adrenal axis in animals exposed to stressers. The authors suggest that the vitamin may be synergistic with cortisone in some of its actions.

BAKER, N.; CHAIKOFF, I. L.; AND SCHUSDEK, A. (*Div. of Physiol., Univ. of California, Sch. of Med., Berkeley*): Effect of fructose on lipogenesis from lactate and acetate in diabetic liver. J. Biol. Chem. *194*:435-43, January 1952.

Lipogenesis from acetate doubly labeled with C^{14}, lactate-2-C^{14}, and C^{14}-glucose was compared in the livers or normal and alloxan-diabetic rats that were fed, for 4 days, a diet containing either 58 per cent glucose or 58 per cent fructuse. In glucose-fed diabetic rats, hepatic lipogenesis from acetate and lactate was greatly depressed, in some cases to one-tenth the normal value. The livers of these rats also lost, almost completely, their capacity to convert glucose to fatty acids.

Fructose feeding restored to the diabetic liver its full capacity to synthesize fatty acids from acetate and lactate—a capacity, the authors note, that occurred without the administration of insulin. This fructose feeding did not repair the defective utilization of C^{14}-glucose in the diabetic liver. This is in contrast to the action of insulin, which has been shown to restore to the diabetic liver its capacity to form fatty acids from glucose as well as from acetate and lactate. On the basis of these findings the authors suggest that impaired lipogenesis from the 2-carbon-like intermediate in the liver of the glucose-fed alloxan-diabetic rat need not be the result of insulin lack per se but may be secondary to the initial or primary block in glucose utilization.

BANERJEE, SACHCHIDANANDA (*Calcutta*): Etiology of diabetes. Calcutta M. J. *49*:39-49, February 1952.

In most instances in man, diabetes mellitus is hypoinsulinism which is produced by increased utilization and destruction, inhibition, or inactivation of insulin in the tissues resulting in diminished circulating insulin. The different observations on the etiology of human diabetes mellitus here presented would indicate that different factors are involved. The etiology of human diabetes is still not known, and the causative factors should also be sought in regions beyond the pancreas.

BAUMAN, EVERETT O. (*Newark, N. J.*): The general practitioner treats the uncomplicated diabetic. J. M. Soc. New Jersey *49*:91-98, March 1952.

With a few basic principles in mind, the average general practitioner can control most uncomplicated diabetics without hospitalization. The basic carbohydrate elements of the diet are used as the foundation, garnished and varied with the low-carbohydrate and substitute foods. The time of action of the various insulins is kept carefully in mind, and the doses are placed in relation to the meals so as to cover the carbohydrate foods and avoid reactions. Finally, the patient is taught by the physician how to give himself injections of insulin and how to test his urine.

BEACH, ELIOT F.; BRADSHAW, PHOEBE J.; AND BLATHERWICK, N. R. (*Biochem. Lab., Metropolitan Life Ins. Co., New York City*): Response to alloxan modified by gonadectomy. Endocrinology *50*:212-17, February 1952.

Castration several months before administration of alloxan fails to eliminate the sex difference in incidence of severe diabetes. Castrated female rats, like intact female rats, more frequently develop alloxan diabetes than do castrated or intact males. However, gonadectomy does show some effects upon the character of alloxan diabetes. Male and female castrate alloxan-diabetics are about equally subject to ketonuria, although there is a marked sex difference in this respect among intact diabetics.

BOAS, ERNST P. (*New York City*): Arteriosclerosis and diabetes. J. Mt. Sinai Hosp. *19*:411-18, July-August 1952.

A statistical study of 500 diabetics over age 40 indicates that, although there is a common association of diabetes and arteriosclerosis (particularly evident in women), the presence of diabetes, even for many years, does not accelerate the progress of arteriosclerosis. Hypertension appears to be more common in diabetic

women than in females in the general population. There is probably a constitutional hereditary basis for the association of these various diseases.

BOOK REVIEW (LAWRENCE, R. D.) (*England*): Treatment of diabetes. Brit. M. J. 2:132-33, July 19, 1952.

The book, *Diabetes Mellitus, Principles and Treatment*, by Garfield G. Duncan and others is reviewed.

BRITISH INSULIN MANUFACTURERS' BIOLOGICAL SUB-COMMITTEE AND THE DEPT. OF BIOLOGICAL STANDARDS, NAT. INST. FOR MED. RES.: The preparation and testing of the provisional British standard for globin zinc insulin. J. Pharm. & Pharmacol. *4*:382-91, June 1952.

The unit potency of globin zinc insulin has been defined as the activity of 0.1163 mg. of the provisional British standard for globin zinc insulin; that is, the solid contains 8.6 British units per milligram. This unit is related to the unit of soluble insulin in that one British unit of activity is the activity of one International unit of soluble insulin after conversion to the British standard for globin zinc insulin.

BROWN, HAROLD; HARGREAVES, HAROLD P.; AND TYLER, FRANK H. (*Vet. Admin. Hosp., and Univ. of Utah Coll. of Med., Salt Lake City*): Islet-cell adenoma of the pancreas: Metabolic studies on a patient treated with corticotropin and cortisone. Arch. Int. Med. *89*: 951-60, June 1952.

A 58-year-old man with hypoglycemia of 8 years' duration secondary to an islet-cell adenoma of the pancreas was successfully treated with corticotropin and cortisone prior to operation. The results of nitrogen-balance studies during cortisone therapy indicate that the correction of hypoglycemia could not be attributed to the protein catabolic effect of the cortisone and was due presumably to an anti-insulin effect in the tissues.

CHOLST, M. R.; LEVITT, LEON M.; AND HANDELSMAN, MILTON B. (*Diabetic Clin., Long Island Coll. Hosp., Dept. of Med., State Univ. of New York Coll. of Medicine in Brooklyn*): Small vessel dysfunction in patients with diabetes mellitus. II. Retinal vessel response in diabetics folowing Priscoline. Am. J. M. Sc. *224*: 39-41, July 1952.

Among 28 diabetic patients who had little or no ophthalmoscopic evidence of vascular sclerosis, who ranged in age from 18 to 69 years, and whose diabetic duration varied from 6 months to 30 years, there were twelve whose retinal vessels exhibited an inability to dilate maximally after intravenous administration of 50 mg. of Priscoline as determined by poor widening of the angioscotoma. Eleven of these 12 patients exhibited exudation in the perimacular region.

No correlation was noted between this "small vessel" dysfunction in the retina and that demonstrated in the skin of the toes of patients with diabetes.

CRAIG, JAMES W.; DRUCKER, WILLIAM R.; MILLER, MAX; OWENS, J. EVAN; WOODWARD, HIRAM, JR.; BROFMAN, BERNARD; AND PRITCHARD, WALTER H. (*Western Reserve Sch. of Med., Cleveland*): Metabolism of fructose by the liver of diabetic and nondiabetic subjects. Proc. Soc. Exper. Biol. & Med. 78:698-702, December, 1951.

The metabolism of fructose in the liver was investigated by hepatic vein catheterization studies in three diabetic patients deprived of insulin and in three nondiabetic subjects. A large hepatic uptake of fructose occurred during the period of intravenous administration in both groups. In all but one case there was a large hepatic output of pyruvic and lactic acid during the fructose infusion. The liver of one diabetic patient in ketosis continued to remove pyruvic and lactic acid from the blood; hepatic glycogen depletion may have accounted for this divergent result. In half the cases (two diabetic patients and one nondiabetic subject) the output of glucose by the liver was increased during fructose administration. The authors conclude that, in the absence of ketosis, the liver of the diabetic subject without insulin metabolized fructose in a manner similar to that of the liver of the nondiabetic individual. The presence of ketosis, however, was accompanied by a decreased output of pyruvic and lactic acid, despite a normal uptake of fructose.

DANA, GEORGE; EVERSOLE STANTON; AND ZUBROD, CHARLES. (*Baltimore*): The clinical entity of retinal aneurysms, glomerular nodules and hyperglycemia. Bull. Johns Hopkins Hosp. *90*:323-26, April 1952. [Abstract of paper presented at the Meeting of the Johns Hopkins Medical Society, January 14, 1952].

A review was made of the charts of all adult patients with diabetes mellitus on whom autopsy was done at

the Johns Hopkins Hospital in the years 1938-1950. Kidney sections of these 190 diabetics were studied independently, and the patients were divided into two groups according to the presence or absence of glomerular nodules. Diabetic acidosis rarely occurred in the 57 patients with glomerular nodules, in contrast to its common occurrence in the 133 controls. Both groups experienced recurrent stress, such as infection, gangrene, and insulin withdrawal. Ninety per cent of the patients with glomerular nodules showed the presence of retinal aneurysms, in contrast to 10 per cent of the controls. It is probable that retinal aneurysms are an intrinsic part of the same entity as glomerular nodules, and it is likely that the primary disturbance consists of aneurysmal dilations of the capillaries. In this series there was no single instance of an acidotic episode in the patients with both retinal aneurysms and glomerular nodules. Since these patients did not develop ketosis in the absence of exogenous insulin, it was concluded that they have an adequate supply of endogenous insulin. It was thought that patients with retinal aneurysms and hyperglycemia would not develop diabetic acidosis when their daily insulin was withheld. In a preliminary clinical study, five typical patients were selected and each studied for 3 to 5 weeks, with no lowering of the carbon dioxide combining power.

DE FILIPPIS, VITO; AND IANNOCCONE, ANGELO. (*Inst. of Medical Semeiology, Univ. of Naples, Italy*): Insulin-neutralizing activity of gamma globulins derived from the serum of an insulin-resistant patient. Lancet 1:1192-93, June 14, 1952.

Gamma globulins isolated from the serum of an insulin-resistant patient protected rats against the hypoglycemic effect of insulin. This fact supports the view that insulin resistance may be due to antibodies for insulin.

DOLGER, HENRY (*Mount Sinai Hosp., New York City*): The management of insulin allergy and insulin resistance in diabetes mellitus. M. Clin. North America 783-90, May 1952.

The author identifies the sources of the various American-manufactured insulins and the sources of their modifiers and discusses their relationship to local cutaneous reactions and to the generalized allergic reactions to insulin. The mild local cutaneous rash almost always disappears on continued insulin injections, i. e., gradual desensitization. The treatment of both types of reactions is also discussed. Insulin resistance is discussed very briefly, touching on the variable etiology. The treatment of such insulin resistance is summarized as consisting "solely in the administration without timidity of as much insulin as is needed to insure adequate utilization of the diet." The frequent reversal to normal levels of insulin requirement after such therapy in the diabetic is mentioned.

DURY, ABRAHAM (*Dorn Lab. for Med. Res., Bradford Hosp., Bradford, Pa.*): Changes in electrolyte and water composition after glucose in unprotected and epinephrine-protected rats. Proc. Soc. Exper. Biol. & Med. 79:315-19, February 1952.

Adrenalectomized rats were given a glucose load per os (2 ml of 50 per cent solution). One group was pretreated with epinephrine (0.04 mg. per 100 gm. wt.) 60 minutes before. Signs of mortal failure (cardiac?) in a large percentage of the non-pretreated series of rats shortly after glucose per os were associated with a significant increase in the plasma potassium concentration, with concomitant ECG changes and a significant decrease in the liver potassium composition only. In the epinephrine-pretreated series a large percentage of the rats survived the glucose load. The levels of potassium in plasma and liver were unchanged from the control values.

EARECKSON, VINCENT O.; and MILLER, JOSEPH M. (*Fort Howard, Md.*): Third-nerve palsy with sparing of pupil in diabetes mellitus: A subsequent identical lesion of the opposite eye. Arch. Ophth. 47:607-10, May 1952.

This is a discussion of the incidence, pathogenesis, frequency, and prognosis of paralysis of the extrinsic ocular muscles as a complication of diabetes mellitus. A case is presented of paralysis of the third cranial nerve of one eye with sparing of the pupil, followed by the paralysis of the third nerve of the other eye with sparing of the pupil. Confusion with aneurysm of the internal carotid artery may exist, especially if the prodromal symptom is pain in or around the involved eye.

EDITORIAL (*London*): Congress of the International Diabetes Federation. Lancet 2:137-38, July 19, 1952.

A report is given on the topics discussed at the first International Congress of the International Diabetes Federation, held at Leiden, Holland, July 7 to 12, 1952.

EDWARDS, SALLY; AND WESTERFELD, W. W. (*State Univ. of New York, Med. Coll. at Syracuse, N.Y.*): Blood and liver glutathione during protein deprivation. Proc. Soc. Exper. Biol. & Med. 79:57-59, January 1952.

A protein-free diet reduced liver glutathione in rats to about 40 per cent of its normal value within 1 to 2 days but did not deplete blood glutathione. The labile 60 per cent of the liver glutathione was lost completely before the liver xanthine oxidase was reduced more than 50 per cent. The residual 40 per cent of the liver glutathione was then retained, whereas the remainder of the xanthine oxidase was lost. Eighty-five to 90 per cent of the glutathione in rat liver was present in the soluble supernatant fraction obtained by centrifuging a homogenate at 30,000 x G.

EPSTEIN, SAMUEL H. (*Boston*): Some clinical aspects of diabetic neuropathy. J. Nerv. & Ment. Dis. *115*: 543-44, June 1952 [Abstract of paper presented at Boston Society of Psychiatry and Neurology, April 18, 1951].

An analysis of 50 cases of diabetic neuropathy was made from the standpoint of the role of vascular disease. There was definite evidences of arteriosclerosis in 25 cases. Elevation of the total protein content of the cerebrospinal fluid was present in 70 per cent of the cases and paralleled the severity of the neuropathy. The prognosis of the neuropathy was much better in the cases without demonstrable evidence of vascular disease. Prolonged poor regulation of the diabetes appeared to play a role in the precipitation or aggravation of the neuropathy in either type. A typical Argyll-Robertson-type pupil may rarely occur in diabetics.

FEINBERG, H.; CHAIKOFF, I. L.; AND ENTENMAN, C. (*Univ. of California Sch. of Med., Berkeley*): Antifatty liver action of papain and ficin in insulin-treated, depancreatized dogs. Proc. Soc. Exper. Biol. & Med. 80: 161-62, May 1952.

The development of fatty liver in insulin-maintained, depancreatized dogs is prevented by the daily administration of the plant proteolytic enzymes, papain and ficin.

FENTON, PAUL F.; DICKSON, HARRISON M.; AND COWGILL, GEORGE R. (*Nutrition Lab., Yale Univ., New Haven, Conn., and Dept. of Biology, Brown Univ., Providence, R. I.*): Glucose absorption in highly inbred strains of mice. Proc. Soc. Exper. Biol. & Med. 80: 86-88, May 1952.

A study was made of glucose absorption from the stomach and intestines in 2 pure strains (C57 and A strains) of mice. Glucose in concentrations of 25, 50, or 75 per cent was administered by tube, and the amount remaining was determined directly at one hour. Increasing the concentration was found to result in an increase in the amount of glucose absorbed. Solutions of 75 per cent concentration were absorbed somewhat more readily by mice of the C57 strain than by those of the A strain. Administration of 25 per cent solutions led to some diminution of the phosphatase activity of the small intestine determined both chemically and cytochemically.

FRASER, ROBERT STEWART (*Dept. of Med., Univ. of Alberta, Edmonton, Alberta, Canada*): Correlation of blood sugar values with glycosuria in diabetics. Minnesota Med. 35:544-46, June 1952.

Blood sugar levels were determined on 22 diabetic patients and one normal person at 7 a.m., 11 a.m., 4 p.m., and 7 p.m. A 24-hour urinary glucose excretion was determined in each case. A qualitative Bendict test for urinary glucose was made each time a blood sugar sample was obtained.

Consideration of the 24-hour urinary glucose excretion alone led to an erroneous conclusion about the state of diabetic control in one third of the cases. If both the fasting blood sugar and the 24-hour urinary glucose excretion were used in this assessment, the state of diabetic control could be correctly determined in all patients. The qualitative Benedict test was found to be an unreliable guide in determining the state of diabetic control. The highest blood sugar value in patients not receiving insulin was most commonly found at 11 a.m.

GIVNER, ISADORE (*New York Soc. for Clin. Ophthalmology):* Report on group survey of diabetes. Am. J. Ophth. *35*:866, June 1952.

A report is made of a group survey by the members of the New York Society which covered a period of 10 months and included 250 cases of diabetes. Although the number of cases was equally divided as to sex, the number showing diabetic retinopathy was about twice as great among the females as among the males. No difference was noted in the development of the retinopathy between myopic and hyperoptic patients. In diabetes occurring in later years, the incidence of retinopathy was less.

GOURLEY, D. R. H. *(Dept. of Pharmacology, Univ. of Virginia Med. Sch., Charlottesville):* Effect of insulin in vitro on phosphate uptake by erythrocytes from diabetic humans. The Scandinavian Journal of Clinical & Laboratory Investigations *4*:79-80, 1952.

In a recent communication, Kvamme has shown that the injection of insulin into humans not only decreased the inorganic phosphate in the plasma and whole blood but also increased the turnover of phosphorus in those acid-soluble organic phosphorus compounds of the cells which are easily hydrolyzable (mostly the labile phosphorus of adenosine triphosphate [ATP]). Invitro experiments of a similar nature were undertaken in this laboratory. With radioactive phosphate being used as a tracer, it was found that addition of 0.05 unit of insulin per cc. of human blood was completely without effect on the rate at which the erythrocytes take up inorganic phosphate ions in vitro. These results did not agree with the results obtained by Kvamme in vivo. However, in the invitro experiments the blood was used immediately after withdrawal from healthy individuals. It seems possible that the lack of effect of exogenous insulin in such blood might be attributed to the presence of endogenous insulin. An attempt has been made to test this possibility by repeating some of the experiments on the blood of untreated diabetic patients which was presumably low in endogenous insulin. In four of the blood samples from diabetic patients the P^{32} uptake of the cells was significantly accelerated by insulin. All but one of these four samples took up P^{32} at a rate lower than normal in the absence of insulin, but in no instance did insulin bring the rate of P^{32} uptake up to that of normal cells. It is difficult to explain why insulin accelerated the rate of P^{32} uptake in some cases but not in all. It may be simply that in only certain samples did there exist a deficit of endogenous insulin with respect to phosphate transfer.

GOVAERTS, P. (*Univ. of Brussels, Belgium*): Physiopathology of glucose excretion by the human kidney. Brit. M. J. 2:175-79, July 26, 1952.

The mechanism of glucose excretion by the human kidney is fundamentally similar to that in amphibians. Mathematical developments have allowed the glomerular filtration to be measured by glucose excretion and the significance of renal diabetes to be appreciated. There remains a wide field to be explored. Among the questions of present interest are included: 1) the precise measurement of the minimal threshold at stated rates of filtration; 2) the influence of the several hormones on the threshold and on the tubular maximal reabsorptive capacity; and 3) the mechanism by which cyanide and other toxic substances disturb glucose excretion.

GRAFE, E.; AND HERING, H. W.: Change from renal diabetes to diabetes mellitus. Klin. Wchnschr. *30*: 345-48, April 15, 1952.

A report is given on two cases, observed for many years, in which typical diabetes renalis in one and a typical renal glycosuria in the other developed into the clinical manifestation of true diabetes mellitus.

HALLAS-MOLLER, K.; PETERSEN, K.; AND SCHLICHTKRULL, J. (*Copenhagen*): Crystalline and amorphous zinc-insulin compounds with prolonged action. Ugesk. f. Laeger *113*:1761-70, December 27, 1951 [Abstr. from J.A.M.A. *149*:617, June 7, 1952].

The authors studied the physiochemical interplay between insulin and zinc and its significance for the action of insulin. The zinc ions affect the solubility of insulin, depending on the *p*H, and cause insolubility at the *p*H of the blood if interfering ions (such as phosphate and citrate) are not present. At neutral *p*H the insolubility is accompanied by a binding of zinc to insulin. The range of activity depends on the form of the insulin (amorphous or cyrstalline), the zinc ion concentration, and other factors and can be varied within wide limits. Clinical tests with zinc-insulin suspensions in diabetic persons confirmed that insulin

preparations with different ranges of activity suitable for clinical application can be produced without the use of such substances as protamine and globin.

HALLAS-MOLLER, K.; JERSILD, M.; PETERSEN, K.; AND SCHLICHTKRULL, J. (*Copenhagen*): Clinical investigations on new insulin preparations with prolonged action: Zinc-insulin preparations used in one daily injection. Ugesk. f. Laeger *113*:1771-82, December 27, 1951 [Abstr. from J.A.M.A. *149*:617, June 7, 1952].

In 65 cases of severe diabetes the authors tested three zinc-insulin preparations with action prolonged for from 18 to over 30 hours. The preliminary results indicate that, even in severe diabetes, satisfactory blood sugar levels can be maintained with one daily injection when these three types of zinc-insulin are available so that a choice can be made.

HANDELSMAN, MILTON B. LEVITT, LEON M.; AND CONRAD, HAROLD, JR. (*Diabetic Clin., Long Island Coll. Hosp., and Dept. of Med., State Univ. of New York Coll. of Med. in Brooklyn*): Small vessel dysfunction in patients with diabetes mellitus. I. Skin temperature response to Priscoline in the toes of diabetics. Am. J. M. Sc. *224*:34-38, July 1952.

In studying vasodilatory effects of drugs on the vessels of the extremities the authors point out that independent variations may occur simultaneously in blood flow to a limb, as determined by the venous occlusion plethysmograph, and in the skin circulation, as measured by changes in skin temperature with a thermocouple. The clinical counterpart of this situation is noted in diabetic patients with superficial gangrene of the toes who have excellent arterial pulsations in the feet and no symptoms suggestive of diminished circulatory efficiency in the extremity.

Of 16 diabetic patients studied by measurement of the skin temperature rise after intravenous injection of 50 mg. of Priscoline, seven exhibited inability of the skin vessels of the toes to dilate maximally. All these patients had excellent pulsation in the dorsalis pedis and posterior tibial arteries and were judged to have normal peripheral circulation. No correlation could be made out between this small vessel dysfunction and the severity or degree of control of the diabetes.

The improvement in peripheral circulation in many patients with diabetes mellitus following the use of a vasodilator like Priscoline cannot be evaluated by skin temperature readings alone.

HARVEY, STEWART C.; WANG, C. Y.; AND NICKERSON, MARK (*Dept. of Pharmacology, Univ. of Utah Coll. of Med., Salt Lake City*): Blockade of epinephrine-induced hyperglycemia. J. Pharmacol. & Exper. Therap. *104*:363-76, March 1952.

Fifteen compounds were studied for their ability to suppress epinephrine-induced hyperglycemia and the pressor response to epinephrine in the rabbit and in the cat. All fifteen compounds manifested some degree of suppression of the hyperglycemia. Thus this property seems to be common to all adrenergic blocking agents, as well as to a variety of agents which do not block other responses to epinephrine. Suppression of epinephrine-induced hyperglycemia generally requires much higher doses of an adrenergic blocking agent than does suppression of epinephrine-induced pressor responses. Ergonovine was found to have hyperglycemia-suppressing activity as doses having no apparent effect on cardiovascular responses to epinephrine. No correlation was observed between the ability to suppress the hyperglycemia and the ability to suppress pressor responses. It seems likely, therefore, that the "hyperglycemia receptors" are different from the "pressor receptors" or that a completely different mechanism of action is involved in the suppression of these two responses.

HAUGAARD, NIELS; and MARSH, JULIAN B. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia*): Effect of insulin on the metabolism of adipose tissue from normal rats. J. Biol. Chem. *194*: 33-40, January 1952.

The metabolism of retroperitoneal adipose tissue from rats fasted 24 hours was studied in vitro by manometric methods. It was found that the addition of insulin in vitro increased the oxygen uptake of this tissue in the presence of glucose, lactate, succinate, pyruvate, or acetate. Insulin decreased the respiratory quotient in the presence of pyruvate but had no effect with the other substrates studied. Insulin was shown to combine chemically with retroperitoneal adipose tissue in a manner similar to that with rat diaphragm. The authors believe that this finding strengthens the concept that the combination of insulin with tissue is a prerequisite for insulin action.

HEINTZELMANN, F. (*Copenhagen*): Cause of death in diabetes mellitus. Ugesk. f. Laeger *114*:555-67, May 1, 1952 [Abstr. from J.A.M.A. *149*:1607, August 23, 1952].

The author has analyzed the causes of 2,260 deaths of diabetics in Denmark in 1947-1949. In most cases, death was due to degenerative heart disorders. This cause of death predominates mainly in the age group of 45 to 64; however, it is an important cause among men in the age group from 15 to 44, in which death is also often caused by renal diseases (more common among men than among women), by tuberculosis, and in a number of cases by the diabetes itself (diabetic coma). The last named is almost exclusively the cause of death among diabetic children. Tuberculosis is the cause of death in diabetics somewhat more often than in the total population; heart disease and arteriosclerosis are the cause much more often; and death from renal disease is relatively frequent among diabetics. Among the oldest diabetics, death from pyelonephritis is more frequent in men than in women.

HERNBERG, C. A. (*Pathological Inst. of the Kantonspital, St. Gallen, Switzerland*): Skeletal changes in adults with diabetes mellitus. Acta med. Scandinav *143*:1-14, May 10, 1952.

Pathoanatomical examination was made of the bone structure of 14 diabetic patients between the ages of 33 and 75. Comparison was made with an equal number of control cases of similar age and sex. Simple osteoblast osteoporosis was found in all cases. In the patients over 65 the diabetics and controls showed the same degree of osteoporosis, whereas in young diabetics the osteoporosis was more severe than in the controls.

HICKS, SAMUEL P. (*Dept. of Pathology, New England Deaconess Hosp. and Harvard Med. Sch., Boston*): Insulin hypoglycemia. J. Pediat. *40*:501, April 1952.

Three pregnant rats, 12 pregnant mice (13 to 21 days gestation and one litter about 8 to 9 days), and several newborn rats and mice were given 2 to 8 units of insulin subcutaneously or intraperitoneally, usually after fasting 12 to 16 hours. All adults developed deep hypoglycemic coma in 3 to 5 hours; then glucose was given which revived all but 2. Twenty-four hours later, adults and fetuses were examined pathologically. All but one adult sustained necrosis of striatal and occasionally cortical neurones. Several fetuses in one litter were dead, and all in another litter had died. Death of fetuses had been recent, for they were fresh and autolysis was absent. All other fetuses escaped injury. In the one litter (near term), in which some animals were recently dead, there was necrosis of the deeper layers of fairly mature cortical nerve cells of the brains of fetuses, with no damage to the outer zone of still developing neroblasts or the periventricular neuroblasts of the deep developing basal ganglia. This pattern was in many respects just the opposite of the pattern of injury from radiation or radiomimetic compounds (mustard, Aminopterin, etc.). In addition, fairly mature nerones in the brain stem and in the cerebellum were necrotic, whereas neroblasts were spared. Similarly, the dorsal fairly mature nerve cells of the cervical cord were necrotic. In substance, the pattern was considerably more like adult hypoglycemic injury than "embryonic" response to radiation. In contrast, one litter, whose age was estimated at 8 to 9 days, showed considerable necrosis of many cells throughout the bodies of the embryos but not especially those of the neuraxis. This generalized "patchy" effect needs further study, as does the whole problem of embryo metabolism during the first third of gestation. Since adult brain damage occurred almost regularly in these experiments and since the neuroblasts escaped, these cells may be said to be resistant to hypoglycemia. Still more significant is the fact that when the fetus is selectively damaged by lack of glucose the neuroblasts are still resistant (despite their rapid growth), whereas the more mature neurons are susceptible. Death of the fetus, without selective damage, as occurred in another younger litter (between 14 and 17 days), is ascribed to an over-all metabolic effect, as occurs with other extreme forms of inhibition. Newborn mice and rats did not become comatose with insulin, but some showed scattered necrotic cortical neurones similar to those seen in adults. Coupling newborn and fetal data, it seems that dependence on glucose in the nervous system increases with maturity of nerve cells, as seems to be the case with oxygen.

HILLS, A. GORMAN; AND STADIE, WILLIAM C. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia*): The effect of combined insulin upon the metabolism of the lactating mammary gland of the rat. J. Biol. Chem. *194*:25-31, January 1952.

Slices of mammary tissue from normal lactating rats

were shown to combine rapidly with insulin. The combined insulin resisted the dissociation action of prolonged washing and caused characteristic increase of the respiratory quotient, indicating synthesis of fat from glucose and acetate. The synthesis of lactose from glucose by mammary tissue occurred in vitro but was not affected by insulin.

HOPKINS, J. GARDNER, WELD, JULIA T., and KESTEN, BEATRICE M. (*Depts. of Dermatology and Pathology, Columbia-Presbyterian Med. Center, New York City*): The treatment of monilia (*Candida albicans*) infections with carbowax-sulfur ointment: A preliminary report. J. Invest. Derm. *18*:419-22, June 1952.

A mixture of carbowax and sulfur in high dilutions inhibits the growth of *Candida* (*Monilia*) *albicans* in vitro. Its application to monilia infections of the skin, nails, and vagina is suggested in view of the encouraging results obtained in 34 patients, several of whom had diabetes.

JACOBS, JAMES S. L.; TEMPEREAU, CLINTON E.; AND WEST, PHILIP M. (*Long Beach Vet. Admin. Hosp., Long Beach, Cal., and Univ. of California Med. Sch., Los Angeles*): The effect of insulin coma on uropepsin excretion. Science *116*:86-87, July 25, 1952.

The problem of evaluating certain adrenocortical functions in schizophrenic psychotics proved to be a difficult one until the discovery of what is evidently a simple and quantitative measure of this activity, namely, uropepsin. Eosinophil counts taken prior to the injection of insulin and immediately after the termination of each treatment revealed changes which consistently indicated adrenocortical stimulation. The consistent daily occurrence of eosinopenia in response to insulin administration implies that the concomitantly increased uropepsin excretion during a course of insulin coma therapy furnishes a quantitative measure of adrenocortical activity.

KAPLAN, H. LELAND (*Houston, Texas*): Diabetes mellitus and atherosclerosis: A review. M. Rec. & Ann. *46*:966-72, May 1952.

The outlook for prevention of the devastating occurrence of atherosclerosis in diabetic patients has been poor. The modern treatment of diabetes, however, should reduce the incidence and severity of vascular complications expected to occur in new diabetics in the next two decades. The brilliant work of Gofman and other investigators in the relationship of cholesterol and atherosclerosis may contribute greatly to the control of this great scourge among diabetic patients.

KNOWLES, HARVEY C., JR.; AND GUEST, GEORGE M. (*Children's Hosp. Res. Foundation, Univ. of Cincinnati*): Tissue electrolytes in alloxan-diabetic rats with ketoacidosis. Proc. Soc. Exper. Biol. & Med., 79:552-54, March 1952.

Data are reported from analyses of tissues of normal rats and of alloxan-diabetic rats with severe ketoacidosis induced by withholding food and insulin 3 to 4 days. In muscle of the diabetic, acidotic rats, compared with that of the normal controls, the concentration of water and of potassium decreased and the concentration of nitrogen increased slightly, with values for sodium and chloride showing no significant change. In liver there was a gain of water, sodium, and nitrogen, with no change in concentration of chloride or potassium. Livers of the acidotic rats showed a greatly increased fat content.

KOBAYASHI, YOSHITO; OHASHI, SHIGERU; AND TAKEUCHI, SETSUYA (*Dept. of Pharmacology, Faculty of Med., Univ. of Tokyo*): Effect of the salts of meso-oxalic acid on alloxan diabetes mellitus. Japanese Journal of Pharmacology *1*:9-21, September 1951.

This report deals with the hypoglycemic effect produced by the salts of *meso*-oxalic acid on the rabbit and dog having alloxan diabetes mellitus. When 100 mg. per kilogram of sodium or calcium salt of *meso*-oxalic acid is given by mouth twice a day to the alloxan-diabetic rabbit (3 hours before and 7 hours after feeding time) for several consecutive days, the sugar in the urine either falls to less than one third or completely disappears. Body weight, on the other hand, increases. In some cases of severe alloxan diabetes in the rabbit there is a decrease or total disappearance of acetone bodies in the blood and a decrease in the sugar and NPN content of the urine, accompanied by a marked drop in the blood sugar level and by gain in weight. The salts of *meso*-oxalic acid have no effect whatsoever on the depancreatized dog.

KOCHAKIAN, CHARLES D.; WRIGHT, PHYLLIS M.; AND ROBERTSON, EVANGELINE (*Dept. of Physiol. and Vital Economics, Sch. of Med. and Dent., Univ. of Rochester, Rochester, N. Y.*): Testosterone propionate and arginase activity in diabetic rats. Arch. Biochem. & Biophys. *36*:221-30, March 1952.

The extra endogenous protein metabolism occurring in phlorhizin and alloxan diabetes did not significantly change the liver arginase activities of normal or castrated adult male rats. Moreover, no correlation between the degree or duration of the diabetes and the enzyme activities of the liver could be detected. Tremendous increases, 400 to 600 per cent, in protein ingestion, however, stimulated identical increases in the arginase activities of the livers of diabetic and nondiabetic rats. Smaller increases, 100 to 200 per cent, produced increases in arginase activity concomitantly with the increase in liver weight. Testosterone propionate did not affect these enzymic changes.

LAWRENCE, R. D. (*Diabetic Dept., King's Coll. Hosp., London*): Insulin hypoglycemia and eosinophilia. Lancet *2*:42, July 5, 1952.

The author cautions that eosinophilia after insulin treatment, as noted recently in a series of mental patients, should not be ascribed to hypoglycemia until local reactions to a foreign injected substance are ruled out.

LAZARUS, SYDNEY S.; AND VOLK, BRUNO W. (*Jewish Sanitorium and Hosp. for Chronic Diseases, Brooklyn, N. Y.*): The estimation of insulin sensitivity by the modified glucose insulin tolerance test. J. Lab. & Clin. Med., *39*:404-13, March 1952.

The Himsworth glucose-insulin tolerance test was modified by administering 0.1 unit of crystalline insulin intravenously 30 minutes after the intravenous injection of 25 gm. of glucose in 50 per cent solution. This procedure elicited a homogenous pattern of response in 40 nondiabetic individuals, the blood sugar falling to the fasting level within 45 minutes after the administration of insulin. With this being used as the criterion for normal insulin sensitivity, 10 of the diabetic patients showed a normal response and 7 patients gave an equivocal response. The authors, however, suggested the rate of decline of the blood sugar level for the 30 minutes after the injection of insulin as an alternative and more exact criterion. The mean value for the nondiabetic controls was 3.8 mg. per cent per minute, with a standard deviation of 0.7 mg. per cent. Of the diabetic patients, 7 had values of less than 2 mg. per cent per minute, and these were considered to be insulin-insensitive. Four patients showed an equivocal response (2 to 2.4 mg. per cent per minute). The remaining 13 patients had values of 2.5 to 5 mg. per cent per minute and were considered to be normally sensitive to the action of insulin. Since these results in the diabetic patients had a nonhomogeneous distribution, the authors believe the test can separate diabetic patients into insulin-sensitive and insulin-insensitive groups.

LEHMANN, H.; AND SILK, E. (*Dept. of Pathology, St. Bartholomew's Hosp., London*): The prevention of color-fading in the Folin and Wu estimation of the blood sugar. Lab. Digest *16*:7, July 1952.

The colorimetric blood sugar estimation of Folin and Wu suffers from the disadvantage that the colors are not stable. The fading on adding water was found to be due to the lowering of the phosphoric acid concentration. It does not take place if the tubes are filled to the mark with an 11.55 per cent (w/v) solution of phosphoric acid. Dilutions to 12.5, 25, or 50 ml. will retain their color at room temperature for more than 8 hours.

LEVY, EDWARD S.; KRAFT, SUMNER C.; AND NECHELES, HEINRICH (*Dept. of Gastro-Intestinal Res., Med. Res. Inst. of Michael Reese Hosp., Chicago*): Chylomicrons in diabetics. J. Appl. Physiol. *4*:848-54, May 1952.

Chylomicrographs and nephelographs on a group of 13 aged diabetic patients were compared with those of a group of 13 aged nondiabetic and 12 young subjects. Distinct differences in the responses of the three groups to graded fat meals were found and discussed. Fat absorption or disposition or both may be different in the diabetic as compared with the nondiabetic aged.

LIPP, G. R. (*Sheffield, England*): Diabetes in infancy. Brit. M. J. *1*:1354, June 21, 1952.

The author comments on a case of diabetes in an infant.

LLEWELLYN, JOHN S. (*Louisville*): Diabetes mellitus in office practice. Kentucky M. J. 50:139-46, April 1952.

Problems relative to diabetes mellitus—diagnosis, general treatment, and care of a limited number of complications—have been discussed.

LOW, BARBARA W. *(Harvard Univ., Cambridge, Mass.):* Orientation of the polypeptide chains in crystals of acid insulin sulfate. Nature, London *169*:955-56, June 7, 1952.

"Air-dried" single crystals of orthorhombic acid insulin sulfate give sharp, somewhat disoriented x-ray diffraction patterns which extend to spacings of approximately 7 A. It can be shown that the simple and gross features of a real structure, such as parallel rods or chains, which are regions of high electron density, will, when favorably oriented, appear as prominent features of high density in the vector structure. The vector structure implies that the real unit cell contains rods or chains of high electron density parallel to the *a*-axis. It seems probable that these are polypeptide chains, folded or coiled in some regular way, which form rodlike structures having a core of high electron density near their center. Sanger found that the insulin molecule of molecular weight 12,000 consisted of four polypeptide chains linked together by disulfide bridges. It seems reasonable to associate each rod in the vector structure with one of those chains, so that the complete molecule would consist of four close-packed chains arranged at the corners of a parallelogram.

MAHL, GEORGE F. (*Yale Univ., New Haven, Conn.*): Relationship betwen acute and chronic fear and the gastric acidity and blood sugar levels in *macaca mulatta* monkeys. Psychosom. Med. *14*:182-210, May-June 1952.

A previous study demonstrated that experimentally produced chronic fear was associated with increased heart rate and increased gastric secretion of hydrochloric acid in dogs. The present study systematically investigated the nature of hydrochloric acid secretion of monkeys in acute and chronic fear. The results confirm the hypothesis that the secretion does not increase during acute fear but does during chronic fear. Blood sugar measurements were also obtained in certain of the experimental conditions. Upon repeated pain-fear stimulation there was a general reduction in blood sugar and a loss in reactivity of blood sugar changes. However, these hypoglycemic changes were not related to the increased hydrochloric acid secretion. The two autonomic processes varied independently. The blood sugar data are ambiguous concerning the mechanism underlying the changes in them.

MANN, MORTIMER *(Indianapolis, Ind.)*: Fundus changes in hypertension and diabetes. M. Times, New York, 80:350-55, June 1952.

The fundus changes which occur in diabetes are further evidence of the vascular damage which will develop in almost every diabetic who lives long enough. All studies indicate that the duration of diabetes plays a dominant role in the development of these lesions. Older patients tend to develop a retinopathy earlier than younger diabetics. Severity of the disease and control do not appear to be important factors. Insulin has made it possible for large numbers of diabetics to live long lives, and the problem of how to protect the diabetic against vascular degeneration remains our challenge.

MARBLE, ALEXANDER *(Boston):* Diabetic coma: Prevention and treatment. J. Michigan M. Soc. *51*:717-21, June 1952.

In the twenty-nine years which have elapsed since the introduction of insulin into clinical use, the morbidity and mortality from diabetic coma have decreased markedly. Prior to 1922, from 40 to over 60 per cent of diabetics who died did so in diabetic coma. At present, less than 2 per cent of deaths among diabetics are in coma. It is the physician's serious responsibility to make the diagnosis early and to institute vigorous treatment promptly. In a known diabetic with a classical history, given by relatives, the diagnosis may be easy. In an unconscious, unidentified patient brought without relatives or friends to the emergency ward of a large city hospital, the recognition of the condition may be more difficult. The patient in diabetic coma belongs in a hospital. Success in treatment depends upon attention to details and upon close, continuous attention of physicians and nurses. In the successful treatment of diabetic coma, constant personal attention of the physician and the fearless use of insulin in adequate dosage are all important. No patient should die in or from diabetic coma unless

there exists an acute complication which in itself is fatal. Deaths due to the fact that patients are not brought for treatment until they are moribund can in time be reduced in number or avoided by continuous education of the patient and his family from the day of diagnosis. A death in diabetic coma is a needless death.

MARGOLIN, MORRIS; AND GENTRY, HAROLD E., JR. (*Dept. of Int. Med., Univ. of Nebraska; Coll. of Med., Omaha*): Clinical evaluation of the Wilkerson-Heftmann blood sugar test, with reference to its use by the general practitioner. Nebraska M. J. 37:139-44, May 1952.

The Wilkerson-Heftman blood sugar test is a rapid, simple, inexpensive, highly accurate, true glucose test. Although providing for only two blood sugar reference levels, it also provides for three clinically significant blood sugar ranges: that of normal and hypoglycemic values, that of satisfactory diabetic control, and that of unsatisfactory and poor diabetic control. The test is useful both as an aid in diagnosis and in the routine management of a majority of diabetic patients. It is recommended as a highly desirable adjunct to the armamentarium of the general practitioner.

MARMER, MILTON J. *(New York Med. Coll., Flower and Fifth Avenue Hosps., New York City):* The use of sciatic nerve block for producing vasodilatation of the lower extremity and comparative study with paravertebral lumbar sympathetic ganglion block. Anesthesiology *13*:207-20, March 1952.

Sciatic nerve block with 10 cc. of 1 per cent procaine produces maximal vasodilatation of the foot which cannot be exceeded and which is seldom equaled by paravertebral lumbar sympathetic ganglion block, as judged by measurement of skin temperature changes. The procedure is easily performed, causes little discomfort, and has been entirely free of complications in the present study of 42 cases and in reports in the literature. Sciatic nerve block may be employed both to relieve intermittent claudication of the foot and to determine the degree of vasoconstrictor tone and the extent of vasodilatation which may be produced by interruption of the sympathetic pathways.

MARTIN, HELEN E.; MEHL, JOHN; AND WERTMAN, MAXINE. *(Univ. of Southern California Sch. of Med., Los Angeles):* Clinical studies of magnesium metabolism. M. Clin. North America 1157-71, July 1952.

The authors discuss the present knowledge of magnesium metabolism, including a part played in coenzyme reactions in both carbohydrate and protein metabolism. Change in magnesium concentration in the blood may vary rapidly by virtue of intracellular and extracellular shift. In diabetic coma the serum magnesium was usually elevated prior to therapy; the reasons for this are not entirely clear. With therapy, the serum magnesium fell in 18 to 24 hours to less than normal levels. Some of the magnesium loss was accounted for in the urine, but not consistently. Other factors, such as hemodilution and intracellular shift following therapy, were considered. Three patients who died had very high serum magnesium levels associated with normal or low potassium levels. These patients died despite heroic therapy. Clinical implication of previous experimental work on dogs regarding magnesium-potassium relationships is discussed, particularly the inability in one case to raise the serum potassium in the presence of a high (tenfold) serum magnesium.

MARTINEZ, CARLOS *(Buenos Aires):* The sulfhydryl groups in experimental diabetes. Acta physiologica latinoamericana *1*:135-62, July 1951.

Some aspects of the importance of sulfhydryl groups in experimental diabetes due to alloxan or pancreatectomy have been studied in the rat and in the toad. The intravenous administration of alloxan in the rat produced (a) a sharp and temporary fall in the sulfhydryl content of blood, liver, kidney, and skeletal muscle; (b) a marked decrease in the sulfhydryl content, in rats with severe diabetes 48 hours and 12 days after alloxan injection. In totally depancreatized diabetic rats and in partially depancreatized rats with mild diabetes, the sulfhydryl content was also lower than in the controls.

The diabetogenic and toxic action of alloxan in the rat could be prevented by intraperitoneal injection of BAL 30 minutes prior to alloxan and by treatment during 12 to 30 days with thiouracil and thiouracil-related compounds. These treatments also hindered the development of diabetes due to partial pancreatectomy in the rat. The same results were obtained by treatment with cysteine, 4-mercapto-2-methylquinazoline and 5-isopropylidene-2, 4-dithiohydantoine. Treatment with propylthiouracil in totally depancreatized, force-fed rats,

maintained with a given dose of insulin, produced a definite remission of glycosuria without loss of body weight. Thyroidectomy and treatment with thiouracil, cysteine. 4-mercapto-2-methylquinazoline, or 5-isopropilidene-2, 4-dithiohydantoine produced a significant increase in the sulfhydryl content in tissues.

MAYER, JEAN; AND BATES, MARGARET W. *(Dept of Nutrition, Harvard Ech. of Pub. Health, Boston):* Blood glucose and food intake in normal and hypophysectomized, alloxan-treated rats. Am. J. Physiol. *168*:812-18, March 1, 1952.

In normal animals, under carefully controlled conditions, two daily subcutaneous injections of glucose (or fructose) and adrenaline, producing hyperglycemia of relatively short duration, caused a statistically significant decrease in food intake, even when the caloric equivalent of the injected glucose and fructuse was taken into account. Conversely, insulin-induced hypoglycemia was accompanied by a significant increase in food intake, even if the doses used were small enough to maintain the blood level at physiological fasting levels. Injections of the substances with no effect on blood glucose (sucrose and fat) had no such effect on food intake. In animals made unable to regulate their blood sugar level by hypophysectomy followed by alloxan treatment, the effect on food intake of prolonged hyperglycemia induced by intraperitoneal glucose administration was even more drastic, causing considerable decrease.

The facts suggest the possibility of a "glucostatic mechanism of regulation of food intake" whereby blood sugar would be the normal stimulus to which hypothalamic or other receptors respond. The application of this concept to the hyperphagia of uncontrolled diabetes is discussed.

MAYER, JEAN; RUSSELL, RUTH E.; BATES, MARGARET W.; AND DICKIE, MARGARET M. *(Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, and Roscoe B. Jackson Mem. Lab., Bar Harbor, Me.):* Basal oxygen consumption of hereditarily obese and diabetic mice. Endrocrinology 50:318-23, March 1952.

A study was conducted of the oxygen consumption of obese and nonobese members of the "Obob" strain of mice. The obese members of this strain were shown to present, in addition to the insulin-resistant type of diabetes and other characteristic symptoms previously described, a very low rate of fasting oxygen consumption. On a body weight basis, their oxygen consumption was less than half that of the nonobese animals; on a body surface basis, their "basal metabolic rate" was lower by more than 40 per cent. When the basal metabolic rate of the obese animals was brought upto nonobese levels by injections of thyroxine, a rapid loss of body weight ensued.

MCCULLAGH, E. PERRY; BECK, JOHN C.; AND SCHAFFENBERG, C. A. *(Dept. of Endrocrinol. Cleveland Clin., Cleveland):* Disappearance of diabetes during estrogen therapy in acromegaly. Cleveland Clin. Quart. *19*:121-26, July 1952.

In a case of acromegaly accompanied by diabetes and arterial hypertension in a 45-year-old woman, administration of estrogen was followed by a shift in the glucose tolerance curve from the diabetic type to complete normality. Reversal of the abnormal glucose tolerance test in acromegaly during estrogen administration is further evidence of a potent hormonal inhibition to the pituitary. This is a clinical demonstration of what has been shown previously in experimental animals. Whether this improvement in carbohydrate metabolism is due to an inhibition of growth hormone or some other pituitary factor is still a matter of conjecture. This case represents the first reported instance of complete reversal of diabetes caused by estrogen in the human. Whether or not the pituitary growth hormone or other pituitary factors have a bearing on the etiology of the average case of clinical diabetes remains for future studies to demonstrate.

MEILMAN, EDWARD; AND ALTSCHULE, MARK D. *(Med. Service and Yamins Res. Lab., Beth Israel Hosp., and Dept. Med., Harvard Med. Sch., Boston.)* Effect of SKF No. 501 (N-9-fluorenyl N, N-ethyl-beta chloroethylamine) on cardiovascular manifestations of hypoglycemia following administration of insulin. Psychosom. Med. *14*:284-86, July-August 1952.

N-9-fluorenyl, N-ethyl-B-chlorotheylamine, a dibenamine congener, does not prevent the adverse effects of insulin-induced hypoglycemia on the heart. Under its influence the increases in heart rate and pulse pressure in hypoglycemic levels are greater than in hypoglycemia produced by insulin alone; feelings of severe anxiety were experienced by normal subjects made hypoglycemic while under the influence of this "adrenolytic" agent.

MORGAN, MARCUS S.; AND PILGRIM, FRANCIS J. *(Mellon Inst., and Western Psychiatric Inst. and Clin., Univ. of Pittsburgh, Pittsburgh, Pa.):* Concentration of a hyperglycemic factor from urine of schizoprenics. Proc. Soc. Exper. Biol. & Med. 79:106-11, January 1952.

The presence of a hyperglycemic factor in the urine of some schizophrenics is confirmed. A scheme for a 15 to 20-fold concentration of the principle is described, and data on the yield and potency of the various fractions isolated are given. Physical and chemical studies of the most active fractions indicate the factor to be a protein, or a material bound thereto. By a comparable fractionation of normal male urine, a measurable quantity of the hyperglycemic factor was not found.

MOSES, CAMPBELL *(Addison H. Gibson Lab., Univ. of Pittsburgh Sch. of Med., Pittsburgh, Pa.):* Dietary cholesterol and atherosclerosis. Am. J. M. Sc. 224:212-18, August 1952.

Accepting as well-founded the relationship of cholesterol to the pathogenesis of atherosclerosis, the author reviews the evidence which implicates exogenous dietary cholesterol in the atherosclerotic process. He concludes that neither moderate increases nor decreases in dietary cholesterol exert consistently significant effects upon blood cholesterol levels and that the almost complete elimination from the diet of all cholesterol and other lipids, including sterol-free vegetable oils, is necessary to effect significant decreases in blood cholesterol. Even in the presence of atherosclerotic disease, the widespread recommendation of such a rigidly restricted diet is unwise because of its unpalatability and the feeding problems it would produce. It is suggested that attention be devoted to other dietary components, especially protein, which may alter the physical state of the circulating cholesterol and thereby influence its relationship to the atherosclerotic process.

MUKHERJEE, S. K.; DE, U. N.; AND SARKAR, D. *(Dept. of Biochem. and Diabetes, Sch. of Trop. Med., Calcutta):* Intravenous glucose tolerance test in normal persons. Indian M. Gaz. 86:494-99, November 1951.

Intravenous glucose tolerance tests were performed on 20 healthy Indians whose ages varied from 25 to 45 years and whose weights varied from 121 to 154 pounds. Thirty cc. of 50 per cent glucose were injected in fasting condition, and the duration of injection was 3 to 5 minutes. The maximum rise of blood sugar took place within 5 minutes after injection. The fall of blood sugar thereafter appeared to take place in two stages: (a) a rapid fall during the first 25 minutes, when the major portion of the injected glucose was removed from the circulation; and (b) a slow and sustained fall during the next 30 minutes. The preglucose fasting level was reached within 50 to 60 minutes after injection. The maximum height of blood sugar was found to be variable, but the time taken for the blood sugar to return to preglucose level was found to be constant in all cases. Glycosuria was found to bear no relation to the height of the blood sugar level.

NABARRO, J. D. N.; SPENCER, A. G.; AND STOWERS, J. M. *(Med. Unit, Univ. Col. Hosp., Med. Sch., London):* Treatment of diabetic ketosis. Lancet 1:983-89, May 17, 1952.

Although ketosis is a common and important complication of diabetes mellitus, its treatment remains controversial. Rational therapy can be founded only on knowledge of the biochemical disturbances that have to be corrected. Insulin should be started as soon as possible, and large doses should be used from the beginning. Rapid reduction of the blood sugar level is essential, and this can be done only if insulin therapy is controlled by frequent estimations of the blood sugar level. Rapid replacement of the extracellular fluid can be achieved by intravenous therapy with a "saline-lactate" solution. There is no definite evidence of the value of intensive alkali therapy, and it may lead to additional metabolic disturbances. Early administration of glucose leads to loss of water and electrolytes in the urine and is contraindicated. It should be given only when the blood sugar level falls. Considerable loss of cellular water, electrolytes, and nitrogen has been demonstrated. In untreated patients, plasma potassium levels are often raised, and potassium-containing solutions should not be given in the early stages. The levels fall soon after the start of treatment with insulin and intravenous fluid, and then solutions containing potassium and other cellular electrolytes should be given. A suitable repair solution is suggested; its administration may be safely started when the blood sugar level begins to fall, and it will prevent the development of severe hypokalemia. When the patient can take fluids by mouth, supplements of potassium phosphate will accelerate the resto-

ration of cellular electrolytes and prevent the accumulation of excess sodium in the cells.

NABARRO, J. D. N.; SPENCER, A. G.; AND STOWERS, J. M. *(Univ. Col. Hosp. Med. Sch., London):* Metabolic studies in severe diabetic ketosis. Quart. J. Med. (New Series) *21*:225-43, April 1952.

Prolonged metabolic balance studies of sodium, potassium, magnesium, chloride, phosphorus, and nitrogen were made on patients recovering from severe diabetic acidosis. Restoration of extracellular fluid was rapid and approximated 20 to 25 per cent of the normal extracellular fluid volume. Glycosuria increased renal losses of water, sodium, and chloride. Cell recovery was slow and was not completed in 10 to 12 days. Differential rates of recovery were found for cell water, intracellular electrolytes, and cell nitrogen.

Supplements of potassium hastened the restoration of this ion to the cells, reduced transfers of sodium into the cells, and prevented the development of serious hypokalemia. The delay in achieving a positive balance for cell nitrogen was related to the comparatively low intake of protein and to overactivity of the adrenal cortex as measured by an increased urinary excretion of reducing steroids. The significance of changes in the plasma levels of potassium, magnesium, and phosphorus are discussed in relation to cell metabolism and renal function.

NATH, MADHAB CHANDRA; AND SAHU, VIRENDRA KUMAR *(Univ. Dept. of Biochemistry, Nagpur, India):* Metabolic relationship between acetoacetate and glucose. Proc. Soc. Exper. Biol. & Med. 79:608-10, April 1952.

The subcutaneous injection of sodium acetoacetate in doses of 50 and 342 mg. per kg. into rabbits caused a rise of 28 and 70 mg. per cent respectively in the blood sugar. Similar injections of glucose in doses of 73 and 496 mg. per kg. produced rises of 13 and 55 mg. per cent in the blood sugar. When both substances were injected simultaneously in the dosage levels shown above, no significant rise in blood sugar resulted. The condensation product of glucose and ethylacetoacetate in equimolecular proportions (223 mg. per kg.) also did not produce a rise. Increased concentrations of sodium acetoacetate inhibited normal glucose utilization when incubated at 37°C. at a *p*H of 7.3 in the presence of rabbit whole blood. The condensation product of glucose and ethylacetoacetate had no effect on the normal ketonemic level and blood sugar tolerance curve of a rabbit.

OAKLEY, WILFRED; AND PEEL, JOHN *(King's Coll. Hosp., London):* Diabetes and pregnancy. Brit. M. J. *1*:1248 June 7, 1952.

The authors decry a recent article in which it was recommended that diabetic pregnancies be allowed to proceed to the onset of spontaneous labor. They point out the higher fetal salvage rate in diabetic pregnancies which are terminated at the 36th week.

OAKLEY, WILFRID *(King's Coll. Hosp., Diabetic Dept., London):* Diabetic emergencies. Practitioner *168*:382-87, April 1952.

Whenever there is the least doubt about the cause of coma in a diabetic, it is a good rule to make the first therapeutic step the administration of glucose without insulin. If coma is due to hypoglycemia, rapid recovery is likely to result; if it is diabetic, no harm will be done.

PALMER, LESTER J.; FLAHERTY, NEIL F.; CRAMPTON, JOSEPH H.; AND JOHNSON, ROGER H. *(Seattle):* The influence of rutin upon diabetic retinitis. Guildcraft *26*:25-28, May 1952.

Thirty-six cases of diabetic retinitis were treated with 60 mg. of rutin four times a day for an average of fifteen months. The retinal picture in eleven patients was unchanged, eight showed improvement, and seventeen were worse. Improvement was not much greater than could be expected under good diabetic control with diet and protamine zinc insulin alone.

PATTERSON, JOHN W. *(Western Reserve Univ. Sch. of Med., Cleveland):* Effect of adrenalectomy on dehydroascorbic acid diabetes. Proc. Soc. Exper. Biol. & Med. 78:758, December 1951.

Dehydroascorbic acid diabetes in rats is ameliorated by bilateral adrenalectomy.

PERLMUTTER, MARTIN; WEISENFELD, SHIRLEY; AND MUFSON, MONROE *(Maimonides Hosp. of Brooklyn and Dept. of Med. N.Y. Univ. Med. Center, New York City)*: Bioassay of insulin in serum using the rat diaphragm. Endocrinology 50:442-55, April 1952.

An attempt was made to adapt the Gemmill technic to clinical use by eliminating the factor of animal insensitivity. The "pooled diaphragm" technic is superior to the "single diaphragm" method in this respect. Normal and diabetic serums do not alter the results of this technic as obtained in Kreb's Ringer-phosphate medium. The elevation in serum insulin content produced by the intravenous injection of 20 units of insulin can be detected 5 minutes after the intravenous injection. Twenty-five gm. of glucose injected intravenously do not cause the secretion of sufficient insulin to be detected by this technic.

PERRY, SEYMOUR M. *(Los Angeles, Cal.)*: Hypopotassemia in diabetic coma. Ann. West. Med. & Surg. 6:520-26, August 1952.

Since all patients in diabetic acidosis and coma have depleted body stores of potassium, regardless of the initial serum potassium, routine parenteral therapy should include potassium. It should be especially intensive in those cases with low initial serum potassium levels. A patient in diabetic coma is not being adequately treated if the physician relies only on blood sugar and carbon dioxide determinations and on tests of the urine. Serum potassium values and/or serial electrocardiograms are important and are the guides to treatment with potassium.

PETERS, JOHN P. *(Dept. of Int. Med., Yale Univ., New Haven, Conn.)*: Diabetic acidosis. Metabolism 1:223-35, May 1952.

Under any immediately conceivable circumstances a certain number of patients will die of acidosis as a result of the infection or other complication which precipitated the acidosis, which is a heavy load for an already sick person. Some will also die because the condition is not detected or treated until the subject has lapsed into irreversible shock. Some of these deaths may be prevented if more attention is given to the causes and the initial course of the condition, emphasized early in this discussion. Mortality will be reduced if recent technical facilities and the latest knowledge about acidosis are utilized. It is an urgent state that cannot be properly managed by prescribed routines. The treatment must be individualized and must be energetically and intelligently conducted. One cannot afford to sleep or even wander far from the bedside until the patient has recovered.

PROUD, J. D. *(London, Canada)*: Diabetic gangrene of the lower extremity. Univ. West Ontario M. J. 22:87-91, June 1952.

The control and treatment of the diabetic gangrene of the lower extremity would seem to consist in prophylactic care, control of the diabetic state, treatment of infection by means of antibiotics and drainage, and, if possible, preservation of a functioning limb. The tremendous difference in the patient's psychological reaction to a local and to a major amputation must be considered. The physician and the surgeon must also realize that this factor plus the patient's age may prevent him from using a prosthesis satisfactorily. The saving of a limb may save the patient from complete invalidism.

RABEN, M. S.; AND WESTERMEYER, V. W. *(New England Center Hosp. and Tufts Coll. Med. Sch., Boston)*: Differentiation of growth hormone from the pituitary factor which produces diabetes. Proc. Soc. Exper. Biol. & Med. 80:83-86, May 1952.

Growth hormone was prepared from a glacial acetic acid extract of anterior pituitary powder. The product was equal in growth-promoting activity to other purified preparations but did not produce diabetes when administered in relatively large doses to dogs, indicating that the diabetogenic factor of the pituitary is distinct from the growth hormone.

RABINOWITCH, I. M. *(Montreal, Quebec)*: The diabetic in industry. Canad. M. A. J. 67:34-41, July 1952

The need for education of the public in the employability of the diabetic is stressed. The various job limitations of diabetics who do and do not take insulin are discussed.

REINBERG, MARTIN H.; GREELEY, PAUL O.; AND LITTLEFIELD, MARY S. *(Los Angeles):* Early diagnosis of diabetes mellitus. J. A. M. A. *148*:1177-81, April 5, 1952.

The importance of early detection and treatment of diabetes mellitus is discussed. To detect early diabetes and to determine the relative value of uncontrolled and controlled screening procedures, a survey for diabetes was conducted among college students. Uncontrolled urine and blood tests were of comparatively little value in this series. A single blood sugar test performed two hours after ingestion of 50 gm. of dextrose is an efficient and simple screening method. A concomitant urinalysis might add to this efficiency. Persons with positive reactions in screening tests may subsequently be studied with glucose tolerance tests, preferably by a "true" blood sugar method. By this means an incidence of 0.45 per cent newly discovered diabetics and 0.71 per cent total diabetics may be expected in a college age group.

RITMILLER, LEROY F.; AND NICODEMUS, ROY E. *(Danville, Pa.)*: Diabetes mellitus complicating pregnancy. Pennsylvania M. J. 55:409-12, May 1952.

From the most recent available statistics, pregnancy occurs in some two thousand diabetic patients every year in the United States. This is a rather small number when one considers the approximate number of known diabetics in the United States to be well over a million. Generally speaking, diabeties is characteristically a disease of the late middle life and thus usually occurs after the childbearing age. There has appeared in several recent publications a growing awareness of the problem in the management of the pregnant diabetic woman and her child. This study re-emphasizes the statement that to achieve an increase in the fetal salvage of pregnant diabetic patients, one must have the meticulous supervision and teamwork of the internist, the obstetrician, and the pediatrician. Whenever one shows laxity in following the basic principles in the management, fetal loss can be expected. It is still impossible to evaluate the efficacy of any individual therapeutic measure. However, there is enough evidence shown in the few cases presented to indicate that frequent hospitalization of the diabetic patient for stabilization and the premature termination of the pregnancy by elective cesarean section are the two measures that have resulted in higher fetal salvage in the experience of the authors.

ROBERTSON, JAMES *(St. Andrew's and St. Clement's Hosps.; and the Diabetic Clins., King's Coll., Willesden General, and St. Bartholomew's Hosps., London):* The practical management of diabetes. Med. Illust. *6*:149-54, April 1952.

The successful management of diabetes depends primarily on the intelligence of the patient and on his willingness to cooperate in the treatment. The patient who cannot grasp the fundamental principles of the treatment will seldom do well; and even though he understands what he should do, he will be in frequent trouble if he lacks the self-control and discipline to do it.

ROCHE, PAT, JR.; CUMMINGS, MARTIN M.; AND HUDGINS, PAUL C. *(V. A. Hosp., Chamblee, Georgia, and Emory Univ. Sch. of Med., Atlanta):* Comparison of experimental tuberculosis in cortisone-treated and alloxan-diabetic albino rats. Am. Rev. Tuberc. *65*:603-11, May 1952.

Rats injected with virulent tubercle bacilli did not die of tuberculosis or develop any progressive infection. A majority of the rats similarly infected but treated with cortisone or rendered diabetic by alloxan either died or developed a progressive tuberculous infection. The influence of cortisone and diabetes on experimental tuberculosis appears to be a lowering of the natural host resistance.

RODRIGUEZ, RICARDO R. *(Buenos Aires)*: The effects of sexual glands and steroids on diabetes in partially pancreatectomized rats. Acta physiol. latinoamericana *1*:226-51, December 1951.

A sex difference in relation to the onset and incidence of diabetes in rates of the same age has been further corroborated. The frequency was much higher in males than in females 6 months after partial pancreatectomy (89 per cent and 27 per cent respectively). An alimentary factor as the exclusive or principal cause of the sex difference can be excluded because this difference persists in experiments in which pancreatectomized rats were pair-fed or forced-fed.

In male rats, simultaneous castration reduced the incidence of diabetes caused by pancreatectomy. If castration was carried out after the onset of diabetes, the diabetes remained unchanged. On the other hand, ovari-

ectomy greatly increased the incidence of pancreatic diabetes. The protective action exerted by the hormone secreted by the ovary in physiological conditions was shown by grafting these organs in the kidney of ovariectomized-pancreatectomized rats; after 6 months a lower incidence of diabetes was shown in these animals, compared with ovariectomized-pancreatectomized controls. In castrated rats after subtotal pancreactectomy, daily injections of estrogens for 6 months had a marked protective action against the onset of diabetes. The following substances were used: estrone, estradiol, diethylstilbestrol,, I-methyl-bisdehydro-doisynolic acid, dienestrol, ethynil estradiol, and ethynil testosterone. Although it had no estrogenic effect, cholesterol also produced a slight but definite decrease in the incidence of diabetes.

This protective action in rats fed ad libitum was also observed in forced-feeding experiments. In this condition, diethylstilbestrol had a marked protective action, preceded in some of the animals by a transitory stage lasting for about 1 month, with an increase of the blood-sugar level and glycosuria; this transitory stage was followed by the permanent protective action which took place in all the diethylstilbestrol-treated rats, with normal values in glycemia and glycosuria, in contrast with the increase of these values observed in noninjected controls. These preventive effects persisted 6 months after the interruption of the treatment wih estrogens. Androgens, on the contrary, increased the incidence and accelerated the onset of diabetes. Substances with progestational activity such as progesterone, corticoids (desoxycorticosterone), and 17 *b*-ethyl-dihydrotestosterone, had no effect on the course of diabetes in the castrated white rats. After 95 per cent pancreatectomy, a compensatory hypertrophy of the insular system was observed histologically; such hypertrophy was similar to that produced in nearly all organs following partial removal of their mass. In the pancreas it was possible to see hypertrophy of the islets of Langerhans; transformation of some centroacinous cells to beta cells, with the granules being well preserved and stained normally; and some sclerosis due to peri-insular growth of connective tissue, with penetration between the islet cells. If the diabetic state did not develop, the compensatory hypertrophy persisted even after 1½ years of the subtotal pancreatectomy, with moderate sclerosis. If diabetes appeared, the hyperglycemia or another unknown factor produced an inhibition of the compensatory hypertrophy followed by insular atrophy and the appearance of degranulated and vacuolized beta cells with pycnotic nuclei. Marked sclerosis, peri-insular and intra-insular, was observed. The gonads and sex hormones played an important part in this compensatory hypertrophy. The androgens interfered with it and for this reason increased the onset and incidence of diabetes. The estrogens, on the contrary, produced hypertrophy and hyperplasia in the old islets and created new ones from the centroacinous cells. This is perhaps the most important cause of the marked protective action on the incidence of diabetes exerted by the ovarian hormones. This hypertrophy and hyperplasia persisted even 6 months after the interruption of the estrogenic treatment. This action was also observed in rats with moderate diabetes, and future experiments will examine the possibility of ameliorating it. Normal rats, guinea pigs, and cats with intrapancreatic implants of estrogens showed, in the beginning, a hyperplasia of the centroacinous cells and, later, newly formed islets containing hypertrophied cells of the beta-cell type. The fact that the formation of new islet tissue was more marked in the zone of estrogenic implantation, and also the normal structure of pituitary and adrenal glands, makes it seem reasonable to suppose that the action of the estrogens upon pancreatic tissue is, partially at least, a direct one.

RODRIGUEZ, RICARDO R.; AND KREHL, WILLARD A. *(Yale Nutrition Lab. Dept. of Physiol. Chem., Yale Univ. Sch. of Med., New Haven, Conn.):* Influence of diet on incidence of alloxan diabetes. Am. J. Physiol. *169*:295-300, May 1952.

A study was made of the toxic and diabetogenic action of alloxan in rats fed natural or synthetic isocaloric diets for one month, and the following results were obtained: The mortality and incidence of diabetes increased in animals fed a low-protein diet and decreased in rats fed a high-protein diet compared with those fed a high-carbohydrate diet. In animals on a high-fat diet, different results were obtained, depending on the type of fat used: a very low incidence of diabetes in rats fed a diet in which the fat is formed primarily by short-chain fatty acids (caprylic acid or coconut oil), and a marked toxicity and diabetogenic action of alloxan in animals fed a high-lard diet (formed primarily by long-chain fatty acids). The high diet in palmitic acid produced hypertrophy of the endocrine tissue of the pancreas and a very low incidence of diabetes. The addition of vitamin E had no influence in this difference regarding the incidence of diabetes.

The different oxidation products of short-chain and long-chain fatty acids and their respective different end pathways in metabolism, with correspondingly different effects on the islets of Langerhans, seem to be responsible for the different toxic and diabetogenic actions of alloxan in these animals.

ROOT, MARY A.; AND CHEN, K. K. *(Res. Labs., Eli Lilly and Company, Indianapolis, Ind.):* Experimental diabetes produced by 8-hydroxyquinoline. J. Pharmacol. & Exper. Therap. *104*:404-11, April 1952.

Intravenous administration of 8-hydroxyquinoline produces pancreatic diabetes in a small percentage of rabbits but not in rats, hamsters, guinea pigs, cats, or dogs. Methylene blue adminstered intravenously immediately before the injection of 8-hydroxyquinoline increases the incidence of diabetes in rabbits. 8-hydroxyquinoline-5-sulfonic acid, 8-chloroquinoline, and 8-methoxyquinoline have no diabetogenic action. A slight, transient hyperglycemia occurs with 2-hydroxyquinoline. Diphenylthiocarbazone produces diabetes in rabbits if a large enough dose can be administered, but the low solubility of this compound makes it difficult to employ.

ROSE, S. *(Dept. of Physiology, Univ. of Melbourne, Australia):* The role of the adrenal cortex in diabetic ketosis. Australian J. Exper. Biol. & M. Sc. *29*:469-75, November 1951.

There is a moderate increase in adrenocortical activity in insulin-controlled alloxan-diabetic rats. There is a very marked increase in adrenocortical activity in uncontrolled alloxan-diabetic, ketotic rats. The insulin resistance and aggravation of diabetes which occur during ketosis are probably related to the increased adrenocortical activity and consequent overproduction of 11-17-oxysteroids. The validity of this casual relationship has been discussed.

SCHACTER, BERNARD; SUPPLEE, HELEN; AND ENTENMAN, CECIL *(Div. of Biological and Medical Sciences, U. S. Naval Radiological Defense Lab., and the Lab. of Experimental Oncology, San Francisco):* Effect of x-radiation and laparotomy on the polysaccharide content of plasma: Relationship to plasma sulfhydryl changes. Am. J. Physiol. *169*:508-10, May 1952.

The effect of total body x-irradiation and of surgical trauma on the plasma polysaccharide (associated with serum protein) was determined in the rat. Following exposure to 700 r x-irradiation, a delayed rise in plasma polysaccharide occurred. After laparotomy, on the other hand, plasma polysaccharide levels were elevated 24 hours later and then returned gradually to normal. It appears that changes in the polysaccharide and sulfhydryl levels of plasma exhibit an inverse parallelism and may be related to tissue proliferation.

SCHACTER, BERNARD; SUPPLEE, HELEN; AND ENTENMAN, CECIL *(Div. of Biological and Medical Sciences, U. S. Naval Radiological Defense Lab., and Lab. of Experimental Oncology, San Francisco)*: Effect of x-radiation, radiomimetic substances and surgical trauma on sulfhydryl content of plasma. Am. J. Physiol. *169*:499-507, May 1952.

Exposure of rats to 700 r total body x-irradiation was followed after several days by a marked decrease in the sulfhydryl content of the plasma. A similarly delayed decrease, of lesser magnitude, was observed after administration of nitrogen mustard and trisethylene triazine at a dose level of 1 mg/kg. body weight. No well-defined plasma sulfhydryl changes were detected during a 6-day period of starvation or after exposure of rats to 300 r total body x-irradiation. Surgical trauma induced by laparotomy led to a significant decrease in plasma sulfhydryl levels by 24 hours after injury, followed by a linear return to normal values over a 12-day period. No significant changes in plasma sulfhydryl levels occurred during the first 12 hours subsequent to laparotomy.

Since the initiation of plasma sulfhydryl changes in the present experiments and acceleration of tissue mitotic activity in similar conditions seem to occur in parallel, it is suggested that decreases in plasma sulfhydryl levels following tissue injury may be indicative of a markedly increased rate of utilization of sulfhydryl groups by regenerating tissue.

SCHANTZ, EDWARD T. *(San Antonio, Texas):* Myasthenia gravis, diabetes mellitus and intraventricular block as co-existent complications of pulmonary tuberculosis. Dis. Chest 22:183-86, August 1952.

A case of pulmonary tuberculosis complicated by myasthenia gravis and diabetes mellitus has been described. It is thought that this is the first case of its type reported in medical literature. There probably is no rela-

tionship between pulmonary tuberculosis and myasthenia gravis.

SELESNICK, SIDNEY *(Dept. of Med., V. A. Hosp., Newington, Conn., and Yale Univ. Sch. of Med.):* Recurrent jaundice in chronic relapsing pancreatitis. Gastroenterology *21*:230-37, June 1952.

Recurrent jaundice in chronic relapsing pancreatitis without associated gall-bladder disease is not rare. Six cases are presented. Obstructive biliary cirrhosis of the liver is a possible serious complication. The normal gall bladder may become secondarily involved in chronic pancreatitis. In persons with chronic pancreatitis, cholecystectomy should not be done except for the same indications one observes in a patient without pancreatitis.

SEN, PARIMAL BIKASH AND BHATTACHARYA, GANGAGOBINDA *(Dept. of Physiol., Univ. Coll. of Sci. and Technol., Calcutta):* Reversal of the diabetogenic action of alloxan by sulfhydryl compounds. Science *115*:41-43, January 11, 1952.

The authors report the reversal of the diabetogenic action of subcutaneous alloxan in rats by the repeated intramuscular administration of either BAL or cysteine at progressive intervals beginning within one hour after the diabetogenic injection of alloxan. On the basis of this work, the authors postulate that the suggested mechanism of the diabetogenic action of alloxan as an inhibition of essential sulfhydryl enzymes is probably not due to the formation of addition compounds between alloxan and the enzymes but rather to the oxidation of essential SH groups to the —S—S— stage. The failure of BAL and cysteine to protect after a time limit of one hour suggests that during this period of time the inhibition of the enzymes was carried to an irreversible state, owing either to further oxidation of SH groups beyond the —S—S— state or to the onset of subsidiary irreversible changes.

SERRE, H.; AND MIROUZE, J. *(Montpellier):* "Pagetic" osteosis in the gouty and diabetic. La presse médicale 60:595-98, April 23, 1952.

After recalling the various mechanisms of Paget's disease, the writers report 6 cases as demonstrative of the part that is held occasionally by the metabolism disorders. Of the 6 cases, 2 were suffering from diabetes and 4 from gout. In all of them the metabolism disorders were long-standing and had very likely preceded the osseous changes by a long time.

SHEPHERD, S. J. JR.; AND BUCHANAN, A. R. *(Univ. of Colorado Sch. of Med., Denver):* Blood glucose levels in alloxan-diabetic rats under combined insulin and ergot alkaloid therapy. Proc. Soc. Exper. Biol. & Med. 78:770-73, December 1951.

A series of alloxan-diabetic rats under insulin therapy was treated with ergotamine tartrate, Hydergine (CCK 179; a mixture of dihydroergocornine, dihydroergokryptine, and dihydroergocristine), and dihydroergocornine (DHO 180) with the following results: Ergotamine tartrate lowered the average blood glucose during a period of 3 to 10 hours after the usual 24-hour protamine insulin injection; dihydrogenated ergot alkaloids (CCK 179 or DHO 180), on the other hand, seemed to have little effect on the blood glucose level as regulated by insulin therapy.

SHEPHERD, STANLEY J., JR.; SMITH, MILLARD J.; AND LONGWELL, BERNARD B. *(Dept. of Biochem., Univ. of Colorado Sch. of Med., Boulder):* The effect of alloxan diabetes on the response of the adrenal gland to cold stress. Endocrinology 50:143-49, February 1952.

The response of the adrenal glands of normal and diabetic rats following exposure to cold was determined by measurement of adrenal cholesterol and ascorbic acid content. Exposure to cold, without preliminary fasting, produced a marked decrease in adrenal cholesterol in the diabetic animals. A comparable decrease was not produced in normal rats by cold unless they had been fasted previously. These results suggest that the response of the adrenal gland to cold, as measured by a decrease in cholesterol concentration, is related to curtailment of metabolically available carbohydrate.

SILIPRANDI, N.; AND NAVAZIO, F. *(Inst. of Biol. Chem., Univ. of Rome):* The action of insulin on blood cocarboxylase in diabetes mellitus. Acta med scandinav *142*:147-48, February 23, 1952.

The authors show that the blood cocarboxylase content in diabetic subjects is lower than in normals. Such a

decrease is generally proportional to the severity of diabetes, as is apparent from a comparison of the cocarboxylase content with the corresponding blood sugar values determined before the injection of insulin. The administration of insulin restores the blood cocarboxylase to normal (that is, to the level in normal subjects) except in the most severe cases of diabetes. The authors affirm that the increase in cocarboxylase after administration of a fixed amount of insulin (20 I.U.) is inversely proportional to the severity of diabetes. In the opinion of the authors, these results strongly indicate that in diabetes mellitus insulin acts on the biosynthesis of cocarboxylase. It thus appears that insulin is necessary for the normal processes of thiamin phosphorylation.

SMITH, M. J. H.; MEADE, B. W.; AND BORNSTEIN, J. *(Dept. of Chem. Path., King's Coll. Hosp. Med. Sch., London):* The effect of salicylate on glycosuria, blood glucose and liver glycogen of the alloxan-diabetic rat. Biochem. J. *51*:18-20, April 1952.

The effect of salicylate on the glycosuria, blood glucose, and liver glycogen content of the alloxan-diabetic rat and on the blood glucose and liver glycogen of the normal rat have been studied. Salicylate reduces the glycosuria and blood glucose in the diabetic rat but causes no change in the liver glycogen content. In the normal rat salicylate causes no alteration in the blood glucose but depresses the liver glycogen content. Possible mechanisms of these changes are discussed.

SOKAL, JOSEPH E. *(Dept. of Physiol. Chem., Yale Univ. Sch. of Med., New Haven, Conn.):* A glycogenolytic factor. I. Effect of liver extract on glycogen stores of rats. J. Biol. Chem. *194*:393-98, January 1952.

The author found that there is present in normal hog liver a substance which, when administered parenterally to rats, produces a striking decline in liver glycogen without depressing muscle glycogen. This action was obtained in adreno-demedullated as well as in normal animals; thus it is considered to be independent of epinephrine and in sharp contrast to the effects of epinephrine on carbohydrate stores. Preliminary fractionation indicates that this glycogenolytic factor is dialyzable, is not a protein or a lipid, and is separable from the antianemia factor. The relationship of the glycogenolytic factor of liver to that in insulin is unknown; they are not identical.

STEINBERG, ARTHUR G.; AND WILDER, RUSSELL M. *(Mayo Clin., Rochester, Minn.):* An analysis of the phenomen of "anticipation" in diabetes mellitus. Ann. Int. Med. *36*:1285-96, May 1952.

Two hundred family histories in which the age of onset of diabetes in parent and child were reported were analyzed for the purpose of examining the validity of the concept of anticipation as a physiological phenomenon in diabetes. The analysis showed that anticipation is a statistical (that is, numerical) and not a biological phenomenon. Accurate predictions, based on the assumption that *there is no physiological relation between the ages of onset in parent and child,* were made of the frequency with which the age of onset would occur in an earlier decade of age in the child than in the parent and of the average difference in age of onset that would be observed in such cases. The predictions agreed with the values obtained from the histories on which this study was based and with those values derived from the studies of Woodyatt and Spetz and of Harris. It is recommended that the term "anticipation" not be used in discussing the observations relating to prior age of onset of diabetes in parent and child and that it be replaced by the more descriptive expression "prior onset," which does not carry with it any of the physiological implications of the former term.

STEPHENS, JOHN W. *(Edmonton, Alberta):* Our present knowledge of potassium in physiological and pathological processes. Canad. M. A. J. *66*:19-32, January 1952.
A review is given noting the causes, symptoms, and manifestations of hyperkalemia and hypokalemia are noted. Particular attention is placed on the causes of serum potassium changes in diabetic coma and on the means of their prevention and correction.

STICKNEY, J. CLIFFORD; NORTHUP, DAVID W.; AND VAN LIERE, EDWARD J. *(Dept. of Physiol., Sch. of Med., West Virginia Univ., Morgantown):* Blood sugar and hemoglobin responses to anoxia in sheep and the effect of acclimatization. Am. J. Physiol. *167*:559-62, December 1951.

Studies have been made of blood sugar and hemoglobin levels in 8 sheep following acute exposures to hypoxia. A statistically significant elevation of blood sugar (10.8 mg. per 100 cc.) during 15 minutes at 303 mm. Hg (24,000 ft.) has been found.

STONER, H. B.; THRELFALL, C. J.; AND GREEN, H. N. *(Dept. of Pathol., Univ. of Sheffield, Birmingham, England):* Studies on the mechanism of shock. Carbohydrate metabolism in nucleotide and ischemic shock. Brit. J. Exper. Path. *33*:131-56, April 1952.

Extensive studies on carbohydrate metabolism in nucleotide and ischemic shock have enabled us to define three stages in the response. The first stage is that of carbohydrate mobilization in which the carbohydrate stores, as a result of reflex stimulation of the adrenal medulla, are converted to glucose and stored in the exracellular space. The second stage is characterized by a decreased rate of glucose utilization, due to inhibition of the early steps in glycolysis, and by gluconeogenesis. This is a further result of enhanced adrenaline secretion, which indirectly stimulates the adrenal cortex, a tissue playing a major part in the reactions of this stage. The features of the third stage, which immediately precedes death, are a fall in blood sugar and a rise in blood lactate probably due to a terminal anoxia. They do not appear to have great general significance and largely represent changes occurring within the blood stream.

STUTINSKY, F.: Potentiating effect of insulin in the normal rabbit. Comptes rendus des séances de la société de biologie et de ses filiales *145*:1014-17, July 1951.

The synergistic action of insulin and vitamins B_1, B_2, and C, as well as of cocarboxylase, on glycemia in the normal rabbit has been confirmed. This property is also manifested by vitamins B_6 and B_{12}, pantothenic acid, adenosine, and adenosine-5-triphosphoric acid. Under the conditions of the author's experiments, all these substances permit a saving in insulin of approximately 25 per cent.

SWINGLE, W. W.; PERLMUTT, JOSEPH; COLLINS, ELLIOTT; SEAY, PATRICK; FEDOR, EDWARD; AND BARLOW, GEORGE *(Biological Lab., Princeton Univ., Princeton, N. J.:)* Effect of intravenous injections of desoxycorticosterone glucoside upon blood glucose of adrenalectomized dogs. Proc. Soc. Exer. Biol. & Med. *78*:865-68, December 1951.

Fasted adrenalectomized dogs of 3 types, 1) in normal health, 2) with mild insufficiency, and 3) in severe adrenal crisis, were injected intravenously with massive (300 to 600-mg.) doses of desoxxycorticosterone glucoside (DCG). Only infrequent rises in blood glucose were observed, and these were associated with marked improvement in the circulation of the animal, increased hydration, increased vigor, and increased muscular activity. A *fasted intact* dog injected with 300 mg. DCG did not show any significant changes in blood sugar level over a 24-hour period. *Adrenalectomized* dogs, presenting severe symptoms but *allowed food* at will during revival from insufficiency, exhibited sharply increased blood glucose levels in the recovery period after DCG administration. The authors do not believe that DCG has any direct action on carbohydrate metabolism but ascribe any blood sugar changes observed to secondary effects on alimentary absorption, circulation, etc.

TAYLOR, R. M.; AND WIGHTMAN, K. J. R. (*Depts. of Med. and Therapeutics, Univ. of Toronto, and Med. Service, Toronto Gen. Hosp.*): Glucose absorption from the duodenum in patients with steatorrhea. Am. J. M. Sc. *224*:190-94, August 1952.

The authors report a significant reduction in absorption of 15 per cent glucose solution in 5 adult patients with steatorrhea of various types. These patients were studied by means of a Miller-Abbott tube, with the balloon occluding the lumen at the duodenojejunal juncture.

THOMPSON, M. D.; AND TROWELL, H. C. (*Mulago Hosp. and Dept. of Med., Makerere Coll., Kampala, Uganda, Africa):* Pancreatic enzyme activity in duodenal contents of children with a type of kwashiorkor. Lancer *1*:1031-35, May 24, 1952.

Pancreatic enzyme activity in duodenal contents was studied in (a) 59 African children suffering from a type of kwashiorkor; and (b) 24 apparently normal African children comparable in age, who formed the control group. The presence of edema without obvious renal or cardiac cause, hair changes, and subnormal weight were the criteria used for the diagnosis of kwashiorkor. In all the children with kwashiorkor the concentration of amylase and lipase in the duodenal contents was well below normal. This defect was reversed in all children who received a high intake of milk protein and in whom intercurrent infections, if present, were treated. The two children with kwashiorkor who did receive milk protein showed no significant rise of enzyme activity in the duodenum and had no clinical improvement, although their intercurrent infections were treated. The possible cause of this de-

pression of enzyme activity and its relation to the illness and its treatment are discussed.

TIETZE, FRANK; AND NEURATH, HANS (*Dept. of Biochem., Univ. of Washington, Seattle*): Light scattering studies on insulin. The minimum molecular weight of insulin. J. Biol. Chem. *194*:1-13, January 1952.

The authors determined the minimum molecular weight of insulin in aqueous solution by a method involving the light scattering of solutions of crystalline zinc insulin. At *p*H 2.6, in the presence of dihydrogen phosphate (extrapolation to zero protein concentration yielded a minimum molecular weight of 12,000 instead of the 6,000 Fredericq and Neurath obtained by using the methods of sedimentation and diffusion. The origin of these discrepancies was considered in the light of the resolving power of the method of light scattering in comparison with the methods of sedimentation and diffusion and osmotic pressure. The authors conclude that the method of light scattering fails to resolve these discrepancies.

TOBIASCH, V. (*Second Med. Clin., Univ. of Frankfurt am Main, Germany*): Attempts of specific therapy in hypophyseal diabetes mellitus. Materia medica Nordmark *4*:78-83, April 1952.

Trials of specific therapy in hypophyseal diabetes mellitus with p-oxypropiophenone are reported. The significance of such treatment in view of experimental and clinical results is briefly discussed.

TOLSTOI, EDWARD (*Cornell Univ. Med. Coll., New York City*): Treatment of diabetic ketosis and coma. M. Clin. North America 767-82, May 1952.

The author places stress on a better understanding of ketogenesis and the treatment of diabetic coma. He presents a practical method for the treatment of diabetic acidosis and coma, using small doses of insulin at one-half-hour intervals so long as the urine contains acetone and sugar. Also along the lines of practical therapy, he discusses parenteral fluids and oral fluids in the further treatment of diabetic acidosis. He emphasizes the principles of therapy rather than the details of an individual regimen and evaluates the use of glucose and potassium salts as aid in the general treatment. A third area of strong emphasis is discussed; namely, the importance of making a careful search for such factors or complications which may initiate coma that causes death, yet which are often amenable to treatment if discovered.

TRAVIA, L.; PELOSIO, C.; AND TOPI, G. C. (*Inst. di Clinica Medica Generale e Terapia Medica dell'Univ. di Roma*): The elimination of free and phosphorylated lactoflavin in diabetes. Acta vitaminologica *2*:66-68, April 1952.

The urinary elimination of lactoflavin fractions (free and phosphorylated lactoflavin) has been studied in diabetic subjects. Whereas there is a greater percentage elimination of free lactoflavin in diabetics in the phase of imbalance (glycosuria, acetonuria, hyperglycemia), there is also a tendency toward the normalization of the ratio of free lactoflavin to phosphorylated lactoflavin in the same subjects with re-established equilibrium of the clinical syndrome (disappearance of acetonuria, and hyperglycemia).

VAN BUCHEM, F. S. P.; and NIEVEEN, J. (*Dept. of Med., Univ. of Groningen, Netherlands*): The simultaneous use of different insulin preparations. Acta med. scandinav. *142*:200-14, March 11, 1952.

With the aid of morning doses of both protamine zinc insulin and di-insulin the authors could often reach a blood sugar level of 100 to 180 mg. per cent during 24 hours. This combination was effective in even severe cases. The amount of protamine zinc insulin has to be sufficient to prevent fasting hyperglycemia while the di-insulin maintains the blood sugar level within normal limits during the daytime. Comparative tests have been done to evaluate the action of di-insulin, globin insulin, and insulin retardol. These have shown that di-insulin and globin insulin have about the same effect; namely, the blood sugar levels are at the lowest point between 12 and 18 hours if the injection is given in the morning and the patient is kept fasting during 24 hours. Earlier results of Bailey and Marble have demonstrated that globin insulin and protamine insulin have a similar effect. Insulin retardol differs from these preparations and is more variable in its action. When globin insulin was substituted in patients whose carbohydrate metabolism had been balanced by di-insulin or protamine insulin and vice versa, these preparations gave about the same effect, although some individual

variations were noticed. By employing a combination of protamine zinc insulin with di-insulin or with any of the other preparations having a similar action or by giving two injections per day of one of the latter preparations, it was possible to reach in the majority of cases the objectives of checking hyperglycemia over 24 hours and the reduction of the number of injections per day.

VAN BUCHEM, F. S. P.; AND NIEVEEN, J. *(Dept. of Med., Univ. of Groningen, The Netherlands):* The basis of the treatment of diabetes mellitus. Acta medica scandinavica *142*:190-99, March 11, 1952.

According to the authors, it is of paramount importance that the object of diabetic control be as close an approximation as possible to the physiological state of carbohydrate metabolism. This is based on experimental data as well as on clinical experience. With this method of treatment, many cases show a marked improvement in carbohydate tolerance so that the insulin dosage can be reduced considerably. Of 321 patients who were treated in the period of 1930-1944, 70, or 22 per cent, finally did not need insulin any longer; 64, or 20 per cent, needed much less insulin; 49 patients, or 15 per cent, who were treated with a diet only showed such an improvement in tolerance that the diet could be increased. One hundred eighty-three patients, or 57 per cent, showed a significant improvement in tolerance; 43, or 13 per cent, neither improved nor deteriorated. Ninety-six patients, or 30 per cent, needed more insulin in the course of treatment. Hypoglycemia in this method of treatment can be prevented by regular control, and it is not imperative to try to reach very low blood sugar values. These may vary from 100 to 180 mg. per cent.

VEGHELYI, PETER V.; KEMENY, TIBOR T.; POZSONYI, JOSEPH; AND SOS, JOSEPH *(Budapest):* Toxic lesions of the pancreas. Am. J. Dis. Child. 80:390-403, September 1950.

Observations on human patients suggest that lesions of the pancreas occur much more frequently than has been supposed. It is surprising, however, to realize with what regularity pancreatic damage can be induced and how sensitive this organ is to different toxic substances. The observation that grave lesions regularly disappear within a short time after discontinuation of the poisoning may account for the fact that pancreatic disease is so rarely diagnosed. Dilatation of the acini, dissociation of the parenchyma, necrosis and subsequent fibrosis were observed in the pancreas of infants dying of dysentery and infantile diarrhea. Similar lesions could be produced in rats by both paradysentery toxin and carbon tetrachloride. There is a discussion of the similarity of the changes to those induced by dietetic means and their possible relation to fibrocystic disease of the pancreas.

VICARI, E. M.; TRACY, A.; and JONGBLOED, A. *(Roscoe B. Jackson Mem. Lab., Bar Harbor, Me.)*: Effect of epinephrine, glucose and certain steroids on fatal convulsive seizures in mice. Proc. Soc. Exper. Biol. & Med. 80:47-50, May 1952.

Convulsive seizures were induced in DBA-strain mice by means of sound, and the protective effects of glucose, epinephrine, and certain steroids were determined. The untreated related animals showed 96 per cent seizure incidence, whereas those treated with epinephrine and glucose showed 6 per cent incidence. Epinephrine with glucose reduced the fatality rate from 79 to 2 per cent. The hormonal compounds, especially testosterone, pregnenolone, and estradiol, were effective in reducing the total seizure incidence from 96 per cent to 15 per cent and the fatal seizure incidence from 79 per cent to 0.2 per cent.

VIETH, GUNTHER *(Hamburg)*: Chemotherapy in tuberculous diabetic patients. Deutsche med. Wchnschr. 77:425-28, April 4, 1952.

Three years of chemotherapy in 72 tuberculous diabetics gave the following results: TB_1 has a moderately adverse effect on metabolism in approximately one third of all patients. These changes can be balanced out with increased insulin doses. The cause of this effect on metabolism is presumed to be a disturbance of glycogen assimilation in the liver cells. PAS has to be discontinued in approximately one fourth of all patients because of intolerance. Half of these patients had alimentary-induced metabolic changes. Chemotherapy for the treatment of tuberculosis is not only justified but necessary in well-controlled diabetics to the same extent as in individuals with normal metabolism.

VOLK, BRUNO W., LAZARUS, SYDNEY S.; AND CO TUI *(Jewish Sanitorium and Hosp. for Chronic Diseases, Brooklyn, N.Y.; and Creedmoor Inst. for Psychobiologic*

Studies, Queens Village, N. Y.): Mechanism of hypoglycemia responsiveness in relation to changes in blood eosinophile level. Proc. Soc. Exper. Biol. & Med. 80: 1-4, May 1952.

The intravenous administration of 0.1 unit of crystalline insulin per kilogram of body weight to the intact anesthetized dog caused an abrupt decline of the blood sugar level, followed within 20 to 45 minutes by a sharp rise. The blood eosinophil level rose significantly, with a peak between 30 and 60 minutes, and returned to normal by the end of 150 minutes. The adrenodemedullated animal showed normal hypoglycemia responsiveness in the insulin tolerance test and an accompanying rise of the eosinophil level similar to that of the intact animal. In adrenalectomized and hypophysectomized dogs a rise of the eosinophil level similar to that of the normal occurred after insulin, even though the blood sugar changes showed no evidence of hypoglycemia responsiveness.

WAGNER, RICHARD (*Boston Floating Hosp., Boston Dispensary, and Dept. of Pediatrics, Tufts Coll. Med. Sch., Boston*): Problems in juvenile diabetes mellitus. J. Mt. Sinai Hosp. *19*:249-55, May-June 1952.

From the psychological point of view, the diabetic juvenile needs more guidance than the nondiabetic. Most of his problems are closely related to stealing food or money in order to buy some of the forbidden fruits, such as candy, ice cream, soft drinks, etc. These transgressions, particularly when occurring in the younger age group, must not be taken too seriously, since they happen more or less in all cases and should be attended to by the physician responsible for the diabetic care. In the adolescent group, other problems become acute. Dietetic excesses, occasionally overcoming the patient like an addiction, are usually of a higher order of magnitude than in the young child. In addition, the physiological emotional instability of puberty is aggravated by the peculiarity of the disease and the artificiality of the existence. The natural separation from the family in this age group and the tendency to become independent lead occasionally to complete refusal of accepting intrafamilial guardianship and to rebellious outbursts against the authority of the parents. It is within the scope of a well-organized social service, familiar with diabetes in childhood and adolescence, to help and even to resort occasionally to placement in a good environment if the family cannot cope with the situation. The mental capacity of juvenile diabetics is within normal range. They are not often of superior intelligence, as was erroneously assumed. However, gross mental retardation is rare, and in general the distribution of mental abilities is comparable to that in a nondiabetic group.

WARTHEN, ROBERT O.; SANFORD, MARSHALL C.; AND RICE, E. CLARENCE (*Washington, D. C.*): Primary malignant tumor of the pancreas in a fifteen-month-old boy. Am. J. Dis. Child. *83*:663-66, May 1952.

A case of primary embryonal cancer of the head and body of the pancreas in a 15-month-old boy is reported. A brief review is made of the eight previously reported primary malignant tumors of the pancreas in infants and children.

WEIGEN, JOHN F.; PENDERGRASS, EUGENE P.; RAVDIN, ISADORE S.; AND MACHELLA, THOMAS E. (*Univ. of Pennsylvania, Philadelphia*): A roentgen study of the effect of total pancreatectomy on the stomach and small intestine of the dog. Radiology *59*:92-102, July 1952.

Hyperglycemia in depancreatized dogs was found to be associated with delayed gastric emptying and with prolonged small-intestinal transit time. Hypoglycemia in depancreatized dogs was associated with a normal and, at times, rapid gastric emptying and small-intestinal transit time. The absence of external secretion of the pancreas from the intestine did not appear to alter the tone or continuity of the small-intestinal pattern or the tone of the proximal colon. Loss of pancreatic function was not shown to alter gastro-intestinal motility while the blood sugar was low; its effects could not be evaluated while the blood sugar was elevated.

WEITZNER, HERBERT A. (*Oakland, Cal.*): Gout and insulin hypoglycemia. Brit. M. J. *1*:1251, June 7, 1952.

Three patients with acute gout (one with chronic tophaceous gout as well) treated with mild insulin hypoglycemia recovered from the acute phase in three to twelve days. Two had histories of one and two attacks yearly, each attack lasting from two to six months. The exact hormonal mechanisms involved are unknown.

WELLER, JOHN M.; AND TAYLOR, ISAAC M. (*Harvard Med. Sch., Boston*): Rate of potassium exchange in the rat erythrocyte. Proc. Soc. Exper. Biol. & Med. 78:780-82, December 1951.

With K^{42} as a tracer, a determination was made of the rate of exchange of potassium in rat whole blood diluted with an isotonic medium containing inorganic salts and glucose. Five per cent of the intracellular postassium of the rat erythrocyte was found to exchange every hour, or 5.2 millimoles of potassium per liter per hour. Two and five-tenths millimols of glucose per liter were utilized every hour. The rat erythrocyte exchanges about 3½ times as much potassium per unit time as does the human erythrocyte. The human erythrocyte utilizes nearly a millimol of glucose for every millimol of potassium that enters the cell. The rat erythrocyte utilizes less than ½ a millimol of glucose for every millimol of potassium that enters the cell.

WHITE, PRISCILLA (*New England Deaconess Hosp., Boston*): The dependence of the physician upon the laboratory in the management of the disease diabetes mellitus. Am. J. M. Technol. 18:140-44, May-June 1952.

Without the medical technologist and the chemical laboratory, physicians could not diagnose diabetes, regulate its treatment, recognize or correct its crises, or prevent its complications. Present-day concepts of these problems are the subject of this discussion.

WINTER, AUGUSTO; VARGAS, LUIS; AND LEWIN, JORGE: Implantation of protamine zinc insulin in infantile and juvenile diabetics. Revista chilena de pediatria. 22:319, August 1951 [Abstr. from Am. J. Dis. Child. 83:829-30, June 1952].

Implants of protamine zinc insulin were done in eight diabetic patients (six children and two adolescents) in order to attain a better control of the disease than that achieved through routine insulin injections. The implants were of either pure protamine zinc insulin or of this drug with added cholesterol; they were placed in the subcutaneous tissues of the infrascapular or gluteal regions. A partial replacement of the daily insulin dose was obtained in three cases; but in the remaining five patients, a total replacement of 20 to 81 days' duration was seen.

WOLMAN, B. (*Dept. of Child Health, Univ. of Manchester*): The function of the adrenal glands in the newborn. Arch. Dis. Childhood 27:283-85, June 1952.

A dose of 5 mg. of ACTH was given to 24 full-term and 12 premature newborn infants, and the changes in circulating eosinophils were measured. Sixteen of the full-term and four of the premature babies showed a normal response, as shown by a 50 per cent decrease in eosinophils on the first day of life. All but two of the remainder showed a normal response on the second day of life. One baby, whose birth weight was 5 pounds 12 ounces, responded on the third day, but an infant born of a diabetic mother did not give a normal response until the end of the first week.

WYATT, C. J., JR. (*Rome*): Management of the diabetic patient. J. M. A. Georgia 41:255-59, June 1952.

After the diagnosis of diabetes has been definitely established, a conference with the patient is advantageous. An air of optimism on the part of the physician is important since the patient is usually discouraged. He may believe that he has a chronic disease for which there is no cure; that he is doomed to a life governed by a strict diet, frequent checking of urine for sugar, and curtailment of normal activities; that if insulin is necessary, it will have to be taken for the rest of his life; and that the cost of the medical care of a diabetic is prohibitive. The patient should be told that 30 to 50 per cent of those who have to be started on insulin are able to discontinue the injections within a reasonable length of time. It is well to emphasize to the patient that the life expectancy of a diabetic is almost as great as the normal life expectancy and that many diabetic patients actually outlive the normal life expectancy. The prognosis for the intelligent and cooperative patient is excellent if the diabetes is identified early and treated diligently by an interested physician.

YOUNG, PETER A.; AND STEWART, G. A. (*The Wellcome Res. Labs., Kent, England*): The distribution of error in mouse insulin assays. J. Pharm. & Pharmacol. 4:169-80, March 1952.

To specify the accuracy of a bio-assay technic, some knowledge of the nature of the distribution of errors between tests of the same type is required, since the

uniformity of variance from test to test, as much as the mean variance, will determine the usefulness of the method. To investigate the distribution of errors in any assay involving a probit response, the mouse insulin test was chosen as being a well-established technic on which many results were available for analysis. The distribution of probits of responses out of 24 to high and low doses of insulin in routine mouse assays is approximately normal. Equally significant positive correlations hold between the responses to standard and unknown samples as between high and low doses. No significant correlation could be detected between the slopes of standard and test within assays, although in the over-all picture the two were parallel. The slope of the assays has been shown to be directly proportional to the body weight of mice, when these have not been used previously. This relationship did not appear to apply to animals used for the second, third, or fourth time.

ZIPF, R. E.; AND WALDO, A. L. (*Biochemical Lab., Miami Valley Hosp., Dayton, Ohio*): Spectrophotometric analysis of carbohydrates and study of anthrone reagent. J. Lab. & Clin. Med. 39:497-502, March 1952.

A description is given of an accurate macrospectrophotometric and microspectrophotometric analysis of glucose or carbohydrate in body fluids or other solutions with the use of the anthrone reagent. The mechanism of the color development was determined. The carbohydrate-furfural derivative condensed with the highly reactive enol tautomer, anthranol.

DIABETES ABSTRACTS ERRATA

p. 311 Kadota, Ichiro; and Midorikawa, Osamu. Delete line 7.

p. 311 Kuntze, Jochim; and Otto, Hellmut. Add after third line; the menopause. The success of treatment, following

p. 316 Reid, E. In bibliographic references, volume and page numbers should read: 8:50-55

p. 317 Ross, E. J. Add to beginning of article: Glucose penetrates into the intraocular fluids from the plasma at a rate which is much faster than that of other

p. 319 Sterling, Rex E.; and Day, Paul L. Title should read: Blood sugar levels and cataract in alloxan-treated, galactose-fed and xylose-fed weanling rats.

p. 400 Friedman, Meyer; Byers, Sanford O.; and Rosenman, Ray H. In bibliographic reference, page numbers should read: 313-15.
In second line, change *tenia* to *temia.*

p. 403 Lopes de Almeida; Ary; and Grossman, Morton I. Change first author's name to Lopes de Almeida, Ary.
In bibliographic reference, page numbers should read: 554-77.

p. 406 Rolland, C. F. Add after word *patients* which begins at end of third line and ends at beginning of fourth line; were over 50 years of age. Gangrene of the foot.
In fourth line delete following: Details are given of a series of 300

EDITORIALS

THE FIRST YEAR OF DIABETES

With this issue, the American Diabetes Association completes the first year of publication of its Journal. It is the hope of the Editors, shared by the Editorial Board and Staff, that DIABETES has measured up to the expectations of the members of the Association and other readers.

The Editors are sincerely interested in receiving comments and constructive criticism in regard to both contents and format as they have appeared during 1952. Contributions will be welcomed whether original scientific papers, review articles, biographical and historical notes, descriptions of technics, or correspondence. Each paper submitted will be studied by selective members of the Editorial Board and, if judged suited to the interests of readers of DIABETES, will be published promptly.

The program of the Annual Meeting of the Association is the main source of the scientific papers published in the Journal. Thus, the Program Committee is in a large measure responsible for the character of the contents of DIABETES. The Committee is conscious of this two-fold responsibility and it also is glad to receive comments in regard to the programs of past years, as well as suggestions in regard to the program of the meeting to be held in New York, May 30 and 31, 1953.

Although not formally announced heretofore, Mr. T. J. Davin has recently been added to the Staff as the new Managing Editor and is demonstrating his ability to continue the high standard previously established by the Journal.

DIABETES has now passed through its phase of infancy. As it matures to meet the challenge of the future, it is hoped that it will serve, with increasing success, physicians and other scientists in their efforts to advance knowledge of disorders of metabolism and especially to promote the welfare of diabetics.

"FREE DIET" FOR DIABETES

The paper by Larsson, Lichtenstein, and Ploman in this issue deals with a controversial subject. Members of the Editorial Board who hold different views present herewith their comments, pro and con.

It should be pointed out that the term "free diet" as used by these authors, has a limited meaning. They do not approve the use of sweets and other dietary indulgences. "Free diet does not mean freedom from control."

PRO

Larsson and Ploman have rendered a notable service in their completion of the paper, which was begun by the late Professor Lichtenstein as a definitive summary of extensive experience in the treatment of juvenile diabetes mellitus in Sweden under a regimen which he inaugurated in his clinic more than twenty years ago.

Since the discovery of insulin, cumulative experience with its use has decreased the disparities that existed among various schemes for diabetic management practiced in different parts of the world. At present, the issues of disagreement among well-qualified clinicians on principles for diabetic management are more apparent than real, with far more points of agreement than of disagreement in their reciprocal criticisms. All agree that the immediate essentials for the treatment of juvenile diabetes are the promotion of good growth and development, strict vigilance during periods of changing insulin requirements to avoid the acute complications of ketonemic acidosis and coma, and the maintenance of a feeling of good health and well-being. Divided opinions on how these objectives can best be attained actually are mainly concerned with the degrees of glycosuria deemed permissable, rather than with details of dietary formulas.

Nearly everywhere, diets now prescribed to be measured for diabetic patients correspond closely in composition and quantity to the diets deemed optimal, from the point of view of nutritionists, for healthy nondiabetic persons of the same age. When normoglycemia is held to be of primary importance, the prescription of a measured diet is desirable, or essential, for the practical purpose of making easier the adjustment of insulin dosage to minimize the risks of hypoglycemic insulin reactions.

The term "free diet" as used by Stolte and Lichtenstein and their many followers has provoked much controversial debate, sometimes stormy and acrimonious. The term itself is ambiguous and inexact, but it has the practical advantage of brevity and wide acceptance with a carefully defined meaning, and its use will probably continue. The term denotes a more or less self-selected diet, unmeasured but eaten within reasonable limits of appetite, and in accordance with family habits and the family table (granted, of course, that the latter is adequate). Those who recommend this so-called unrestricted normal dietary regimen have repeatedly stated that they do not condone reckless excesses or gross irregularities in eating habits. Lichtenstein reported long ago that such self-selection of food among his patients led to an average total consumption which, over considerable periods of time, corresponded closely to the amounts that might have been prescribed to be measured and eaten each day. With food intake varying according to appetite, however, insulin dosage must be adjusted frequently to allow continuous, or almost continuous, glycosuria as a safeguard against hypoglycemic reactions and also to avoid excessive glycosuria (with attendant polyuria) and to avoid the development of ketonuria. So far as the immediate consequences of such a regimen are concerned, there is abundant evidence that hyperglycemia per se does not lead to acute manifestations of metabolic imbalance. Metabolic balance studies on diabetic subjects over short periods of time have shown that the anabolic effects of insulin will sustain positive balances (i.e., storage) of nitrogen and minerals needed for growth despite continuous glycosuria; further evidence on this point is afforded by the records of excellent growth and development throughout childhood among the patients reported by Lichtenstein and his co-workers.

Opinions differ as to what etiologic factors are involved in the slow evolution of the late complications of degenerative disease in diabetic patients, and as to whether long-continued hyperglycemia is in fact a critical factor. The classification of patients into categories according to the degree of "control" is fraught with the obvious possibility of errors of interpretation when investigators differ in their definitions as to what constitutes good or bad clinical control; also, when there is so much uncertainty regarding the conduct of patients during periods of self-management when not under close medical supervision. Among such groups it is obvious that many factors other than mere levels of glycemia or glycosuria are operative. Clinical practices in diabetic management, both with and without strict dietary supervision, have greatly improved and the hazards of infection have greatly diminished during the past ten years—or even five years—with the advent of antibiotic- and chemo-therapy. It is likely that another twenty years of observation may be necessary for adequate evaluation of this important problem.

—GEORGE M. GUEST, M.D.

CON

One welcomes to DIABETES the contribution of Larsson and Ploman from Lichtenstein's clinic in Stockholm because the paper provokes discussion as to the best type of dietary treatment for diabetic patients not only in childhood but also in later life. It is refreshing to note that the authors encourage their patients not to indulge in excesses or gross irregularities in diet. However, proponents of the "free" or "unrestricted normal" diet would admit that, despite a certain amount of standardization and uniformity which may develop naturally after a time, there is inevitably more variation in food intake from day to day on such a program than

if definite amounts of food are prescribed. Furthermore, with less restricted diets, patients are more apt to take concentrated carbohydrate in forms difficult for even the best controlled diabetic to utilize.

Diets for diabetic children and adults should be thoroughly adequate particularly as regards protein, minerals, vitamins and calories. This can be arranged without difficulty by definite dietary prescriptions in which the amount of carbohydrate and of total calories are kept within certain reasonable bounds. The uniformity and constancy from day to day which follow allow a much better opportunity for establishing the insulin requirement than does the variability of the unrestricted diet.

It is natural that those clinicians who advocate free or unrestricted normal diets also maintain that hyperglycemia and glycosuria are not harmful as long as ketosis is avoided. Furthermore, often they teach that the late cardio-vascular-renal and nervous system complications of diabetes are not preventible by careful control of the diabetic state but that they will occur anyway after a sufficient number of years of diabetes.

At the outset, it must be stated clearly that the main point is not whether hyperglycemia and glycosuria are in themselves harmful. They may well be injurious because of disturbances in fluid and electrolyte balances which they cause. However, the chief reason for directing attention to hyperglycemia and glycosuria is that they are convenient and reliable indicators of underlying metabolic abnormalities. They are way-stations on the road to ketosis. The clinician must decide whether he will set as his goal the mere avoidance of ketosis or whether he will attempt to approach the normal more closely by avoiding also hyperglycemia and glycosuria in so far as practicable.

To find reliable answers to the basic questions which have been raised, it is not enough to follow children over 5, 10 or even up to 15 years of diabetes and to be impressed that during such periods those under observation appear to be well and to have developed properly. One must take pains to follow such patients over 15, 20, 25 or 30 years of diabetes and at the end of these long periods attempt to discover whether those patients who have maintained the best control of diabetes have the least complications in the vascular and nervous systems and those whose control has been poorest have the most extensive complications. One cannot draw valid conclusions from a single patient or from small numbers of patients but when truly large groups with onset of diabetes under the age of 25 years and duration of the disease over 15 years are studied, the conclusion is inescapable that consistently poor control usually brings a high incidence of retinitis, nephropathy, vascular calcification and neuropathy. On the other hand, careful control usually brings the reward of relative freedom from complications.

Proponents of the free diet maintain that psychologic trauma is lessened when patients are allowed a free choice of food and permitted to live an unhampered life. This may be true to some extent but often this aspect of the problem is overemphasized. At any rate, in the long run, such deleterious effects as these are of minor importance when compared to the physical damage seen after many years of poor control. Nothing is more disheartening than to see an individual in his thirties or forties who after 15 or more years of diabetes is blind or nearly so and has extensive vascular-renal disease with hypertension and nephropathy.

Uncontrolled diabetes is not a benign condition. It is a foe worthy of respect. Based on painstaking studies of large groups of patients, the conviction is growing that proper treatment consists in the supplying of a thoroughly adequate yet carefully controlled diet with sufficient insulin to keep the blood sugar as nearly normal and the urine as nearly free from sugar, as is possible without producing frequent or severe insulin reactions. "Ideal" control is practically unattainable with the means of treatment now available; of necessity one achieves varying degrees of partially adequate control. However, although one rarely if ever achieves the ideal, if one sets a lower goal, the results are almost certain to be less satisfactory.

—ALEXANDER MARBLE, M.D.

THE MENTION OF DIABETES

The advertisers, as well as the contributors and readers of a magazine, administer to its success.

To those firms who shared our confidence in the appeal and acceptance of DIABETES during its first year, we offer our appreciation.

Members of the ADA and readers who find information in these pages are aware of the contribution which these advertisers make to our common goal of disseminating knowledge of the nature, diagnosis, and treatment of diabetes and its complications to the practicing physician.

When corresponding with advertisers, mention of the fact that their message has been seen in DIABETES can do much to confirm their opinion of this magazine as a medium reaching physicians and scientists in this and other countries.

Apollinaire Bouchardat
1806 - 1886

Elliott P. Joslin, M.D.
BOSTON, MASSACHUSETTS

Bouchardat's life and soul were wrapped up in the problems of diabetes and diabetics. Until his buoyant and enthusiastic entrance upon the stage, diabetes was universally considered a fatal, a deadly, a hopeless disease. Over and over again, Bouchardat emphasized this fact and then went on to say that it was his purpose to show the contrary and to proclaim that, barring serious complications, diabetics could live as long as most people, the strict hygienic regime which they were obliged to follow counterbalancing the handicap of the disease. Above all else, Bouchardat was the apostle of hope in a diabetic world of despair.

Bouchardat grasped the fundamental point that glycosuria had its origin in the sugar of the blood, which in turn came chiefly from carbohydrate in the diet, from bread and cereals—although he recognized, as his contemporary Claude Bernard was then demonstrating in his laboratory in Paris, that it could be derived from protein. Bouchardat urged his patients to make their own analysis of the sugar-producing content of a food by eating it and then testing their own urine. In this way Bouchardat introduced into diabetic therapy the personal responsibility of the patient in his own treatment. This was one of his cardinal contributions. At first his patients made their tests for glucose with unslaked lime. Later he employed a copper reagent anticipating Fehling's test. Fortunately, he was able to make quantitative tests of the glucose excreted in a given period by taking advantage of Biot's discovery of the polariscope and thus compute carbohydrate intake and outgo.

No disease, according to Bouchardat, was more apt to relapse than diabetes. He cites the example of a man who became free from diabetes for ten years until at the age of eighty it reappeared, thus illustrating the insidious onset and sly return of the malady.

Although Bouchardat devised all sorts of measures to make the forbidding, nauseating, rancid meat-fat diet of Rollo palatable, he never lost sight of the fact that the aim of treatment was to keep the urine sugar free. Primarily he lowered the carbohydrate in the diet by his limitation of bread and the exclusion of milk. He introduced the use of gluten bread, but he had no illusions regarding it. He did not want to be called a "gluten bread doctor." He advocated moderation in its use as well as of all foods in treatment. *"Mangez le moins possible."* He noted the favorable effect of undernutrition during the Siege of Paris. He occasionally fasted a patient. He emphasized green vegetables and even washed them to lower the carbohydrate.

Bouchardat was the first to utilize exercise to control the glycosuria. He pushed this to the limit in season and out of season. He taught his patients to exercise particularly the muscles of the arms and chest, because thereby he hoped to improve the strength of respiration. He explained in many ways to his patients the good effect of exercise, and in support of it he cited the high incidence of diabetes among the professional classes in contrast to that among manual workers.

He recognized that the mental capacity of the patients was retained long after the loss of muscular and nervous power, though he admits that the memories of his patients suffered. He observed the diminution and

occasional regain of sexual activity both in males and females, although he stated in his first edition in 1875 and again in the second in 1883: "1. *Les femmes atteintes de vrai diabète sucré deviennent très-rarement enceintes.* 2. *Dans le nombre si considérable de diabétiques qui sont venus me consulter, je n'ai pas mémoire d'avoir vu une seule femme enceinte.*"

Apollinaire Bouchardat was Professor of Hygiene in the University of Paris. He was a friend of Claude Bernard, who over and over again in his *Leçons sur le Diabète* calls attention to Bouchardat's activities in the experimental field and his conceptions of the etiology of diabetes, although he does not mention his clinical activities. This is not strange, because Claude Bernard's work was confined to the laboratory. He was concerned with his discoveries of 1) curare glycosuria, 2) the glycosuria following the puncture of the 4th ventricle, 3) the invention of a method to estimate the sugar in the blood, 4) the changes that followed in the sugar content of the blood in the right heart upon the exclusive feeding of protein to dogs, 5) the discovery of glycogen in the liver and its glycogenic function and the disappearance of glycogen after death, as a result of a diastatic enzyme. Claude Bernard held the liver as the organ primarily concerned with diabetes. He does not appear to have been interested in the treatment of the diabetic and actually contributed nothing directly to it.

Bouchardat suspected the pancreas as the cause of diabetes. He was the first to attempt to prove this by its removal, but surgery then was too crude. Bouchardat was a good chemist. He noted the difference in action between glucose and levulose and tried to make use of the latter's peculiar behavior as well as that of its precursor, insulin, in the control of the disease. He recognized inosite and various other carbohydrates. Both clinically and chemically he observed acetone in the breath and urine of his patients with severe diabetes, but did not clearly associate it with diabetic coma although recognizing coma could be precipitated in such cases and for them he prescribed relaxation. He determined the intake and excretion of carbon dioxide and pointed out the advantages of potassium in the low carbohydrate vegetables.

Although he knew alcohol was not directly sugar producing, more and more as he grew older he restricted its use.

Bouchardat examined the blood for sugar, even though to carry out the test it required 300 cubic centimeters. He explained why it was that glycosuria could be high and glycemia low, because in one the percentage found in the urine represented the quantity secreted by the kidney during an average period of several hours but with the other it was the analysis of the existing sugar in the blood for the moment. In emphasizing the frequency and ready detection of diabetes he related how even a hotel bell-boy had diagnosed the disease in an old man by observing the white spots on his pants which would not brush off or disappear with benzine, but would wash off with water.

It is a great pleasure to have the photograph of Bouchardat (from which the cover drawing was made) which came to me through the friendly intervention of Mrs. William B. Bell and Mr. Maurice Paz, Président de L'Association Française de Diabétiques through the assistance of Professor and Mrs. Boulin, who succeeded Professor Labbé, in charge of the Hopital de la Pitié in Paris. It appears that Apollinaire Bouchardat's granddaughter married Professor Francis Rathery, whose *Diabète Sucré, Leçons Cliniques* in 1934 and 1935 I received from him and prized. It was eventually through their son, Dr. Michel Rathery at the Hopital Bichat that the picture was obtained.

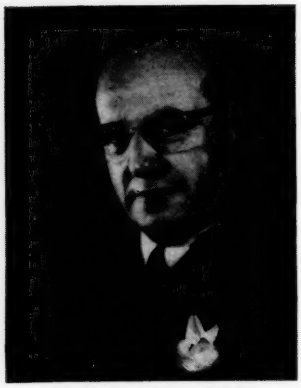
When anyone attempts to write an account of an historical period or phase in diabetes, he invariably becomes indebted to Dr. Frederick M. Allen, whose detailed compilation of the story first appeared in 1919 in the Rockefeller Monograph, entitled *Total Dietary Regulation in the Treatment of Diabetes* by Allen, Stillman and Fitz. This monograph is now out of print. What a contribution to the world it would be if Dr. Allen would amplify it and publish it so that the material, which he so painstakingly gathered years ago, could be available to us all. I hope this year at the annual meeting of the American Diabetes Association action can be taken to encourage Dr. Allen to fulfill this task. No one else in the world could do it as well.

Bouchardat wrote simply and clearly. His French is therefore easy to read. I wish that space permitted quoting some of the sentences which constantly are in my mind. It is most unfortunate that his monograph was not translated immediately into English, because thereby in this country we failed to benefit from it for almost two generations.

Apollinaire Bouchardat was born in 1806 and died in 1886. He was buried in Paris in Père LaChaise cemetery. Would that his spirit might know the gratitude of millions of diabetics whose lives he prolonged and made endurable and to whom he gave, and still gives, courage and hope.

The Song of Diabetes

This ingenious poem, in the manner of Longfellow's "Hiawatha," was read by its author, Dr. Cecil Striker, at the Banquet of the 12th Annual Meeting of the ADA in Chicago, June 7, 1952.



CECIL STRIKER, M.D.

In the office of the doctor,
In the sanctum of the specialist,
Sat the diabetic patient.
Seven cardinal symptoms had he,
Seven means of recognition.
High blood sugar, malnutrition,
Nagging weakness, all these had he,
Polydypsia, polyuria,
Polyphagia, glycosuria,
And the doctor started speaking,
"I am here to guide and warn you,
Here to treat you and instruct you.
Two great friends have diabetes,
Singled out from all the others.
Basic therapy is diet,
Insulin when indicated.
Some there are, who need no insulin;
Diet only may control them.
Magic savior is insulin
For those others who require it.

Follow faithfully your orders,
Comrade make, of diabetes,
Working with it, not against it,
Thus avoiding psychic conflict.
Life expectancy is lengthened,
Yea, assured is normal living!
T'was not always so, my patient,
In the days before Minkowski,
In the days of poor prognosis,
In the days before von Noorden.
Long before the days of these men,
Claude Bernard, experimentor,
Studied enzymes of digestion,
Medullary sugar center,
Store of glycogen by liver,
Fathered modern physiology,
Paved the way for later research,
For all those who followed after.

Many men there were who labored
On the puzzle of the pancreas.
There was Max von Pettenkofer
Classical investigator,
Carl von Voit on dietetics,
Rubner of the calorimeter,
Heat and energy he measured,
Lusk and Benedict his followers;
Langerhans for islands noted.
Kussmaul recognized air-hunger,
Labeled now as Kussmaul breathing.
Naunyn, coiner of a new word,
Coined the new word, acidosis;
Magnus-Levy treated coma;
Emil Fischer, noted chemist,
Henry Sherman for nutrition.
These were men who laid the background,
Pioneers, these research giants;
Built the bridge between the patient
And the laboratory findings."

When the patient left his office,
Long the doctor sat and pondered
On the cause of glycosuria,
On the function of the liver.
Fate of glycogen he pondered,
On cholesterol reflected.
D:N ratio he thought of,
Ketone bodies, oxysteroids.
Factors chemical he mused on,
On this segment of the problem.
Thought then, of another segment,
Of the role of the adrenal,
Of hypophysis secretion.
Pancreas beta cells considered
And the alpha cell production;
Of the mystery of the granules.
Thyroid, ovaries and testes,
How essential their secretions.
All the endocrines considered
And the need for homeostasis.

As he mused thus, meditative,
Science spoke then, to the doctor;
Spoke to him of diabetes
And of all its complications,
Sending terror to its victims,
Sending grief and death among them.
Spoke to him of acidosis,
Painted him a vivid picture
Of the patient acidotic,
Of the patient sorely suffering;
Hard his breath came through his nostrils,
Through his teeth he buzzed and muttered.
Retinopathy depicted,
Dreaded macular involvement,

With its tragic blinded victims
Hearing voices call in darkness.
And arteriosclerosis
With its manifold involvements,
Such as striking early onset,
Of diseases coronary.

Then of legs and feet spoke science,
Spoke of crippling claudication,
Of restricted ambulation,
Painful, cramping, locomotion;
Of the failure to recover
From a superficial trauma;
Deeper, deeper, damage spreading,
Patient plagued by fear of gangrene;
With the sloughing wound enlarging,
Pain and apprehension mingled,
Who, by doubt and anguish tortured,
Then presented serious problems.
Spoke of worsened diabetes,
Spoke of worsened minor lesions,
Then of diabetic gangrene,
Gangrene with its poor prognosis.
Spoke of need for amputation
And the points of amputation;
Mentioned Lisfranc, subpatellar,
And the higher mid-thigh region.

Warned of kidney complications,
Of severe albuminuria,
Casts, edema, and uremia,
Kimmelstiel, their designation.
Warned of insulin reaction
With pre-prandial cephalgia;
With diplopia and confusion,
Cold and clammy perspiration,
Dizziness with wheeling, whirling,
Whirling, round and round,
and downward.
Loss of consciousness may follow
Sometimes death, alas, ensuing.
Miscellaneous others mentioned,
Carbuncle, pruritus vulvae,
Painful osteoporosis,
And peripheral neuritis.

Sad, the doctor as he listened,
Sad, because of dismal warnings,
Still, he smiled when he remembered
All the tools at his disposal.
Thought of insulin, rejoicing,
Of the men who gave it to us;
Paused to cheer for Best and Banting,
Names to celebrate forever!
From the snares of previous failures,
From the case report of Barron,
Came the concept of extraction.
All alone worked Best and Banting,
Labored long and tedious hours.
From tenacity came triumph,
Came the joy of isolation,
Came the proof, the confirmation.
Thought then of the work of Joslin
With his passion for perfection,
Indefatigable worker
With unquenchable endurance;
With meticulous instruction
For strict control of patients, and
Statistical analysis
Of clinical material.
Thought of other great clinicians,
Thought of scientific methods,
Thought of work in laboratories,
Thought of all the dietitians.

And the doctor's grateful spirit
Set him in a mood for singing:
"Sing, oh song of diabetes
Of the happy days to follow,
In the land of glycosuria,
In the pleasant land and peaceful.
Sing the mysteries of the pancreas,
Sing the blessings of the insulins;
Buried is dread malnutrition,
Buried is starvation diet,
Buried hypoproteinemia,
Massive hepar is forgotten."
Hailed the use of all the insulins
And gave thanks for their inventors,
Thankful for their skill and wisdom,
Thankful too, for new improvements.
Protamine and NPH with
Prolonged action in the body,
These discovered by the scholar
Hagedorn, the sage of Denmark.
Cheered the gratifying prospect
For the diabetic children,
For their rehabilitation,
Normal growth, and good nutrition;
Cheered the child who takes his hypo,
And his fine cooperation;
Doomed, before, to rapid wasting,
Cheered because that child is living.
And he hailed a great achievement:
Pregnancy of diabetics,
Long a sad and sorry story,
Now, a joyous, safe experience,
As the faithful diabetic
Bears a child unto her husband,
With the beauty of its mother,
And the vigor of its father.

Then the doctor, looking forward,
Looking, then, toward future progress,
Dreamed of greater knowledge, insight,
Into diabetic problems.
Dreamed a dream of insulin, of
Molecule complex and heavy,
Of its structural arrangement,
Of its chemical components.
Abel isolated sulphur;
Might more fractions be discovered,
Fractions which might be effective
In the treatment of the patient?
Might not synthesis be realized,
Oral insulin perfected,
Newer chemicals discovered
Finding cause for diabetes?
Dreamed of chemistry of glucose
And of energy production;
Of the metabolic process,
Tissue chemistry, and enzymes.
Dreamed of new and complex factors,
Of the role of hexose phosphate
In obscure phosphorylation;
Mystery of deamination;
Of sulphydryl radical with
Its importance undetermined,
Future place of isotopes, of
Glutathione and alloxan.

All these ideas, all these problems
Thoughtful doctors have in common;
All the members of this conclave,
Making A.D.A. their symbol.
Bound together, dedicated,
Organized to help the patient,
Organized to teach the doctor,
A.D.A. their torch resplendent!

—CECIL STRIKER, M.D.
Cincinnati, O.

Postgraduate Course

in DIABETES and BASIC METABOLIC PROBLEMS

Directed by CHARLES H. BEST, M.D.

January 19, 20, and 21, 1953 At Toronto, Canada

The first Postgraduate Course in Diabetes and Basic Metabolism Problems will be conducted by the American Diabetes Association under the direction of Charles H. Best, C.B.E., M.D., F.R.S., Director of the Banting and Best Department of Medical Research of the University of Toronto, on January 19, 20 and 21, 1953, at the University of Toronto.

Developed by the Association's Committee on Postgraduate Education, under the chairmanship of Edward L. Bortz, M.D., the Course will have as its Clinical Director, Ray F. Farquharson, M.B., Professor of Medicine of the University of Toronto, and Andrew L. Chute, M.D., Professor of Pediatrics of the University of Toronto, will act as Associate Clinical Director.

The Course is open to members of the Association and the medical profession. The maximum number of registrants accommodated will be 100; minimal registration 25.

FEES: $20 for the three-day Course to members of the American Diabetes Association; $40 for non-members. The full fee shall be paid at the time of filing application for the Course and will be returnable by the Association to any registrant who submits his withdrawal in writing not later than January 5.

REGISTRATION: Applications for registration may be obtained from J. Richard Connelly, Executive Director, American Diabetes Association, Inc., 11 West 42 St., New York 36, N. Y. Registrations will be accepted in the order received with preference given to members of the Association. All registrations will be officially confirmed.

HOTEL ACCOMMODATIONS: Information as to hotel accommodations in Toronto will be sent to registrants with their matriculation card confirming acceptance for the Course.

THE FOLLOWING TOPICS AND DISCUSSIONS (SUBJECT TO CHANGE) WILL BE COVERED DURING THE 3-DAY COURSE.

MONDAY MORNING, JANUARY 19

9:00 Registration
Ray F. Farquharson, M.B., Chairman
Manifestations of Diabetes

9:30 Clinical—Howard F. Root, M.D.
10:00 Pathological—J. D. Hamilton, M.D.
10:30 Intermission
10:45 Clinical features of diabetic acidosis and coma—E. Perry McCullagh, M.D.
11:05 Electrolyte metabolism in diabetic acidosis—Randall G. Sprague, M.D.
11:25 Treatment of coma—Herbert Pollack, M.D.
11:45 Round-table Discussion—Howard F. Root, M.D., Chairman; Doctors Randall G. Sprague, George M. Guest, Herbert Pollack, Henry B. Mulholland

AFTERNOON Frank N. Allan, M.D., Chairman

2:00 Experimental diabetes—Francis D. W. Lukens, M.D.
2:30 The adrenals in relation to diabetes—Jerome W. Conn, M.D.
3:00 Intermission
3:15 The action of insulin—Charles H. Best, M.D.
3:45 Cholesterol—Henry T. Ricketts, M.D.
4:15 Round-table Discussion—Charles H. Best, M.D., Chairman; Doctors Francis D. W. Lukens, Jerome W. Conn, Randall G. Sprague, E. Perry McCullagh, Henry T. Ricketts

EVENING

6:00 Social Hour
7:00 Dinner
8:00 Travelogue—Charles H. Best, M.D.

TUESDAY MORNING, JANUARY 20
Edward L. Bortz, M.D., Chairman
Complications of diabetes

9:30 Cardiovascular complications—Howard F. Root, M.D.
10:00 Ocular complications—John C. McCulloch, M.D.
10:30 Neurological complications—H. J. M. Barnett, M.D.
11:00 Intermission
11:15 Infectious complications—Francis D. W. Lukens, M.D.
11:45 Errors in treatment—Henry B. Mulholland, M.D.

12:15 Round-table Discussion—Francis D. W. Lukens, M.D., Chairman; Doctors Howard F. Root, John C. McCulloch, H. J. M. Barnett, Henry B. Mulholland

AFTERNOON Arthur R. Colwell, M.D., Chairman

2:00 Management of diabetes in infancy—Robert L. Jackson, M.D.

2:20 Management of diabetes in childhood—Andrew L. Chute, M.D.

2:40 The prognosis in juvenile diabetes—W. T. W. Clarke, M.D.

3:00 Acidosis in children—George M. Guest, M.D.

3:20 Intermission

3:35 Problems in insulin therapy, including allergy and resistance—Arthur R. Colwell, M.D.

4:05 Insurance for diabetics—R. C. Montgomery, M.B.

WEDNESDAY MORNING, JANUARY 21

Andrew L. Chute, M.D., Chairman

Management of diabetes

9:30 Diabetes control—Edward L. Bortz, M.D.

10:00 Dietary instruction—Deaconess Maude Behrman

10:30 Properties of the different insulins—A. M. Fisher, Ph.D.

11:00 Intermission

11:15 Clinical use of insulin—Arthur R. Colwell, M.D.

11:45 Surgical problems in diabetes—D. W. G. Murray, M.B.

12:15 Round-table Discussion—Edward L. Bortz, M.D., Chairman

AFTERNOON Charles H. Best, M.D., Chairman

2:00 Hyperinsulinism—W. R. Campbell, M.D.

2:30 Hypoglycemia—neurological manifestations—J. C. Richardson, M.D.

3:00 Intermission

3:15 Factors affecting the Islands of Langerhans—R. E. Haist, M.D.

3:30 Insulin content of pancreas—G. A. Wrenshall, Ph.D.

3:45 Visit to the Department of Medical Research—Charles H. Best, M.D.

FACULTY OF THE POSTGRADUATE COURSE

FRANK N. ALLAN, M.D., *Executive Director, Medical Department, Lahey Clinic, Boston, Massachusetts*

H. J. M. BARNETT, M.D., *Clinical Teacher in Medicine, University of Toronto; Assistant Physician, Toronto General Hospital*

DEACONESS MAUDE BEHRMAN, *Director, Dietary Department, Lankenau Hospital, Philadelphia, Pennsylvania*

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RAY F. FARQUHARSON, M.B., *Professor of Medicine, University of Toronto; Physician-in-Chief, Toronto General Hospital*

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ASSOCIATION NEWS

THIRTEENTH ANNUAL MEETING

The next Annual Meeting of the American Diabetes Association will be held May 30-31, 1953 at New York City. The Meeting, as customary, will precede the Annual Session of the American Medical Association, June 1-5. A. D. A. headquarters will be at the Hotel Commodore and information relative to hotel accommodations and reservations will be sent to the membership in the near future.

LEGION d' HONNEUR FOR DOCTOR GUEST

Dr. George M. Guest of Cincinnati became a Chevalier of the Legion d'Honneur of the French Government "for meritorious services in education and international understanding and for his outstanding researches in pediatrics." The decoration was presented to Doctor Guest in Chicago on September 27 by French Consul General Monsieur Francois Briere. Doctor Guest is a member of the International Children's Center, whose headquarters is in Paris, and where he has frequently conducted courses in pediatrics.

RECEPTION FOR DR. AND MRS. JOSLIN

More than 500 physicians, associates, former patients and neighbors attended a golden wedding reception for Dr. and Mrs. Elliott P. Joslin at their home in Oxford, Massachusetts, on September 13, according to the Boston Sunday Globe of September 14.

Prior to the reception several hundred persons attended ceremonies at the newly-renovated Public Health Service Diabetes Study Center, located in the Oxford Town Hall, which was rededicated in honor of Dr. Joslin.

Dr. and Mrs. Joslin were escorted from their home to the Town Hall by the local American Legion post. There, the Legion Medal for Americanism was awarded to Dr. Joslin, "for his help in establishing the Clara Barton Diabetic Camp for Girls nearby and a similar camp for boys in Charlton, Massachusetts, which bears his name."

Dr. Hugh L. C. Wilkerson, Chief of the Diabetes Section of the Public Health Service paid tribute to Dr. Joslin, "for an unselfish lifelong career, dedicated to the capture and arrest of dreaded diabetes."

Later, during the reception on the lawn of the Joslin home Mrs. Joslin was presented with a wedding ring clock made of gold.

THE CHARLES H. BEST INSTITUTE

The Board of Governors and the Senate of the University of Toronto announced the laying of the corner-stone of the Charles H. Best Institute, at College Street and Queens Park, Toronto, Ontario on November 7, 1952.

This building, when completed, will be devoted to teaching and research in physiology at the University of Toronto. Following the ceremony, which included an academic procession, there was a reception in the Library of the Banting Institute.

OBITUARIES

BENJAMIN DAVIDSON, M. D., of Brooklyn, New York, a member of the American Diabetes Association since 1941, died in Maimonides Hospital, Brooklyn, on July 6, 1952 at the age of 67 of mycardial infarction. A graduate of Cornell University Medical College, he had been certified by the American Board of Internal Medicine and devoted much of his practice to the problems of diabetes and metabolic disorders.

Doctor Davidson was in charge of the Diabetes Clinic of Beth Moses Hospital in Brooklyn and was Chief of the Diabetes Clinic of The Good Samaritan Hospital in New York City.

EARL WILLIAM SHAFFER, M. D. of Chicago, a member of the American Diabetes Association since July, 1949, died there on September 2, 1952, of cerebral hemorrhage at the age of 60.

After receiving his B. S. at Illinois College in 1916, he completed his medical training at Rush Medical College in 1922 and interned at Cook County Hospital for the following two years. He had been certified by the American Board of Internal Medicine and was an associate on the medical staff of Ravenswood Hospital, Chicago, from 1925 to 1944 and was senior member of the medical attending staff from 1944 until the time of his death. He had been a senior partner of the Marshall Field Clinic from the time of its organization.

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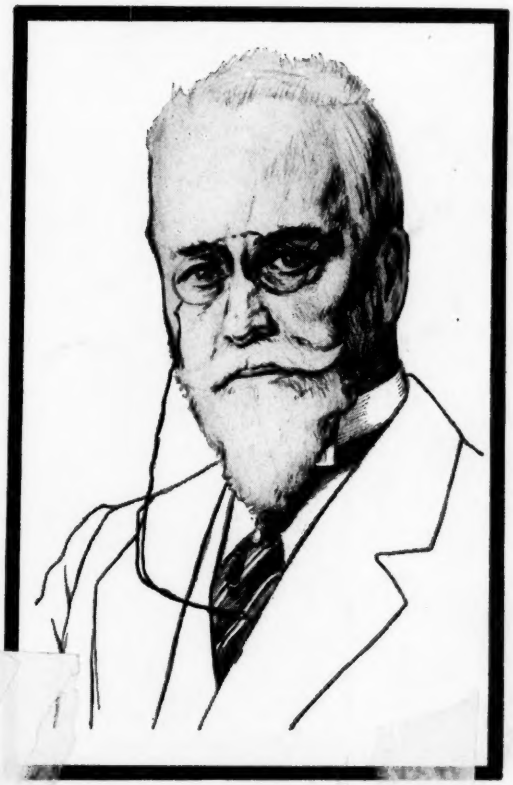

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LONG TYPE

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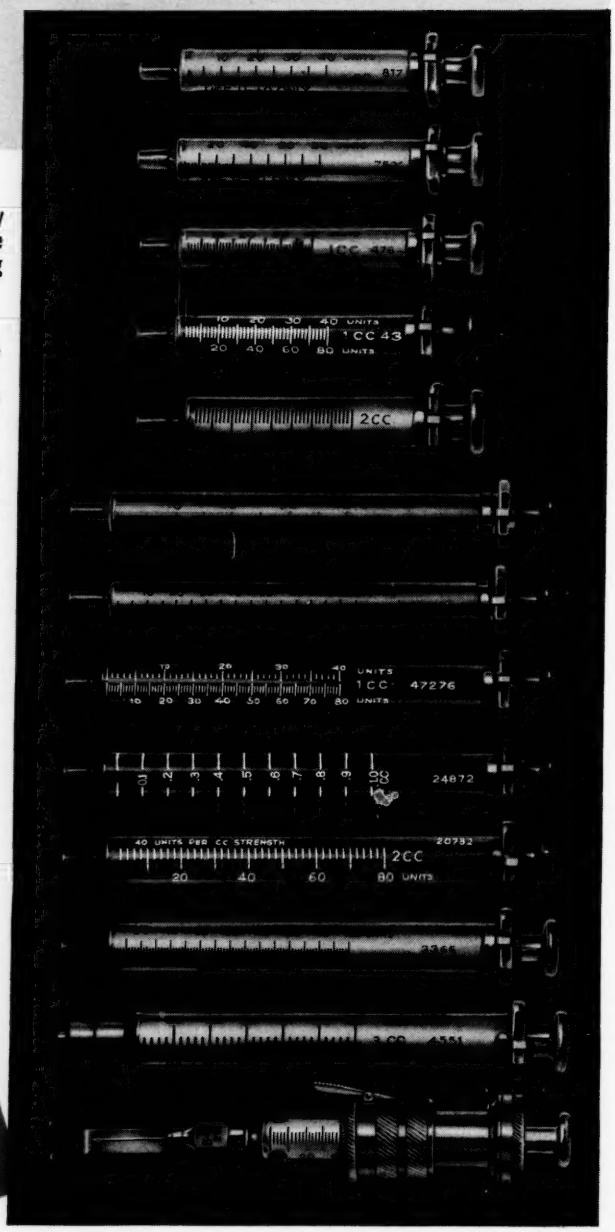

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1YBI-40-80	B-D Yale, blue plunger, 1 cc. in 40-80 Unit
2YZ	B-D Yale 2 cc. in 80 Units of 40 Unit strength

LONG TYPE

1YTI-40S	B-D Yale, blue plunger, 1 cc. U40 only, single scale in red
1YTI-80S	B-D Yale, blue plunger, 1 cc. U80 only, single scale in green
1YTI-40-80	B-D Yale, blue plunger, 1 cc. in 40-80 Unit
1YU	B-D Yale, blue plunger, 1 cc. in 1/10 cc.
2YPZ	B-D Yale, blue plunger, 2 cc. in 80 Units of 40 Unit strength
2YPI-80S	B-D Yale 2 cc. U80 only, single scale in green
3YLH	B-D Yale Luer-Lok Syringe 3 cc. for 40-100 Unit strength
40	B-D Busher Automatic Injector

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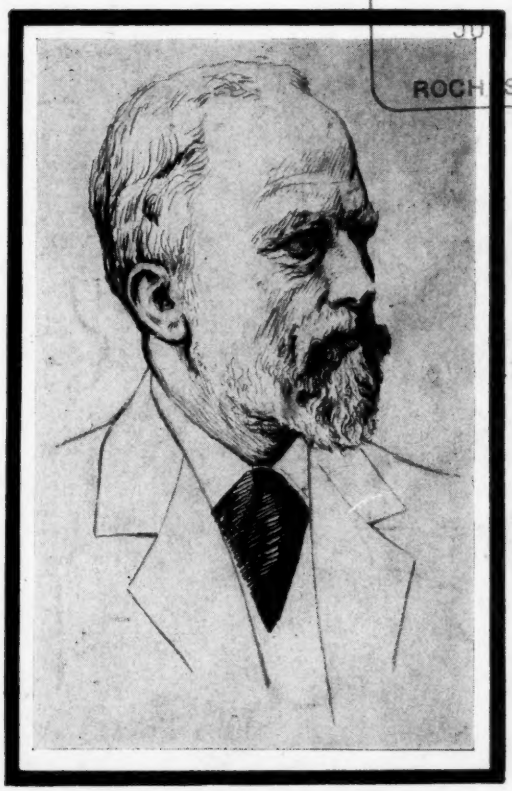

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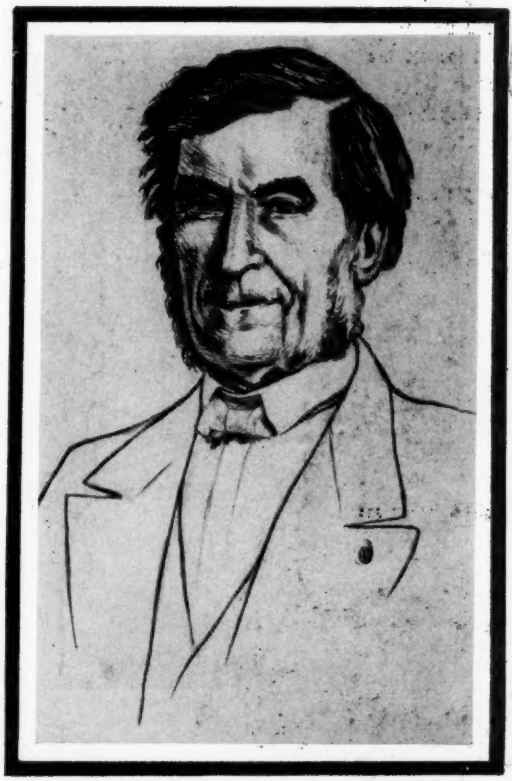

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